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| (54) Title: HUMAN PROTEINS HAVING TRANSMEMBRANE DOMAINS AND DNAs ENCODING THESE PROTEINS (57) Abstract A protein comprising any of the amino acid sequences represented by Sequence Nos. 1 to 9, a DNA coding for said protein, exemplified by a cDNA comprising any of the base sequences represented by Sequence Nos. 10 to 18, and an expression vector of said cDNA as well as an eucaryotic cell expressing said cDNA. Said protein and eucaryotic cell having said protein on the membrane surface can be provided by expression of a cDNA coding for a human protein having a transmembrane domain and of a recombinant of the human cDNA. | | |

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DESCRIPTION

HUMAN PROTEINS HAVING TRANSMEMBRANE
DOMAINS AND DNAs ENCODING THESE PROTEINS

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TECHNICAL FIELD

The present invention relates to human proteins having transmembrane domains, cDNAs coding for these proteins, and expression vectors of said cDNAs as well as eucaryotic cells
10 expressing said cDNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against said proteins. The human cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy. Furthermore,
15 the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by said cDNAs. Cells, wherein these membrane protein genes are introduced and membrane proteins are expressed in large amounts, can be utilized for detection of the corresponding ligands, screening
20 of novel low-molecular pharmaceuticals, and so on.

BACKGROUND ART

Membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. in the material
25 transportation and the information transmission which are mediated by the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino acids, and so on, where
30 the genes of many of them have been cloned already.

It has been clarified that abnormalities of these membrane proteins are associated with a number of hitherto-

cryptogenic diseases. For instance, a gene of a membrane protein having twelve transmembrane domains was identified as the gene responsible for cystic fibrosis [Rommens, J. M. et al., Science 245: 1059-1065 (1989)]. In addition, it has been clarified that several membrane proteins act as receptors when a virus infects the cells. For instance, HIV-1 is revealed to infect into the cells through mediation of a membrane protein fusin having a membrane protein on the T-cell membrane, a CD-4 antigen, and seven transmembrane domains [Feng, Y. et al., Science 272: 872-877 (1996)]. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification, many membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises transfection of a cDNA library in eucaryotic cells to express cDNAs and then detection of the cells expressing the target membrane protein on the membrane by an immunological technique using an antibody or a physiological technique on the change in the membrane permeability. However, this method is applicable only to cloning of a gene of a membrane protein with a known function.

In general, membrane proteins possess hydrophobic transmembrane domains inside the proteins, wherein, after synthesis thereof in the ribosome, these domains remain in the phospholipid membrane to be trapped in the membrane. Accordingly, the evidence of the cDNA for encoding the membrane protein is provided by determination of the whole base sequence of a full-length cDNA followed by detection of highly hydrophobic transmembrane domains in the amino acid sequence of the protein encoded by said cDNA.

DISCLOSURE OF INVENTION

The object of the present invention is to provide novel human proteins having transmembrane domains, DNAs coding for said proteins, and expression vectors of said DNAs as well as transformation eucaryotic cells that are capable of expressing said DNAs.

As the result of intensive studies, the present inventors have been successful in cloning of cDNAs coding for proteins having transmembrane domains from the human full-length cDNA bank, thereby completing the present invention. In other words, the present invention provides human proteins having transmembrane domains, namely proteins containing any of the amino acid sequences represented by Sequence Nos. 1 to 9. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs containing any of the base sequences represented by Sequence Nos. 10 to 19, 21, 23, 25, 27, 29, 31, 33 and 35, as well as expression vectors that are capable of expressing any of said DNAs by in vitro translation or in eucaryotic cells and transformation eucaryotic cells that are capable of expressing said DNAs and of producing the above-mentioned proteins.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02000.

Fig. 2: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02061.

Fig. 3: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by

clone HP02163.

Fig. 4: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02219.

5 Fig. 5: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02256.

Fig. 6: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10390.

Fig. 7: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10474.

15 Fig. 8: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10527.

Fig. 9: A figure depicting the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10528.

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BEST MODE FOR CARRYING OUT THE INVENTION

The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the transmembrane domains of the present invention, wherein the method for obtainment by the recombinant DNA technology is employed preferably. For instance, in vitro expression of the prot ins can be achieved by preparation of an RNA by in vitro transcription from a vector having one of cDNAs of the present invention, followed by in vitro translation using this RNA as a

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template. Also, recombination of the translation region into a suitable expression vector by the method known in the art leads to expression of a large amount of the encoded protein by using prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

In the case in which one of the proteins of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro, when the translation region of said cDNA is subjected to recombination to a vector having an RNA polymerase promoter, followed by addition to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, containing an RNA polymerase corresponding to the promoter. RNA polymerase inhibitors are exemplified by T7, T3, SP6, and the like. The vectors containing these RNA polymerase inhibitors are exemplified by pKA1, pCDM8, pT3/7 18, pT7/3 19, pBluescript II, and so on. Furthermore, a membrane protein of the present invention can be expressed as the form incorporated in the microsome membrane, when a dog pancreas microsome or the like is added into the reaction system.

In the case in which a protein of the present invention is produced by expressing the DNA using a microorganism such as *Escherichia coli* etc., a recombinant expression vector bearing the translation region in the cDNA of the present invention is constructed in an expression vector having an origin, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator etc., which can be replicated in the microorganism, and, after transformation of the host cells with said expression vector, the thus-obtained transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the microorganism. In this case, a protein

fragment containing an optional region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind an optional translation region. Alternatively, a fusion protein with another protein can be expressed. Only a protein portion coding for said cDNA can be obtained by cleavage of said fusion protein with a suitable protease. The expression vector for *Escherichia coli* is exemplified by the pUC system, pBluescript II, the pET expression system, the pGEX expression system, and so on.

In the case in which one of the proteins of the present invention is produced by expressing the DNA in eucaryotic cells, the protein of the present invention can be produced as a transmembrane protein on the cell-membrane surface, when the translation region of said cDNA is subjected to recombination to an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) insertion site, etc., followed by introduction into the eucaryotic cells. The expression vector is exemplified by pKAl, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian culture cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, etc., budding yeasts, fission yeasts, silkworm cells, *Xenopus laevis* egg cells, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the present proteins on the membrane surface. The expression vector can be introduced in the eucaryotic cells by methods known in the art such as the electroporation method, the potassium phosphate method, the liposome method, the DEAE-dextran method, and so on.

After one of the proteins of the present invention is expressed in prokaryotic cells or eucaryotic cells, the

objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea or a surface-active agent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

10 The proteins of the present invention include peptide fragments (more than 5 amino acid residues) containing any partial amino acid sequence in the amino acid sequences represented by Sequence Nos. 1 to 9. These peptide fragments can be utilized as antigens for preparation of antibodies.

15 Hereupon, among the proteins of the present invention, those having the signal sequence are secreted in the form of maturation proteins on the surface of the cells, after the signal sequences are removed. Therefore, these maturation proteins shall come within the scope of the present invention.

20 The N-terminal amino acid sequences of the maturation proteins can be easily identified by using the method for the cleavage-site determination in a signal sequence [Japanese Patent Kokai Publication No. 1996-187100]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. When sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins wherein sugar chains are added.

25 Accordingly, such proteins or peptides wherein sugar chains are added shall come within the scope of the present invention.

30 Accordingly, such proteins or peptides wherein sugar chains are added shall come within the scope of the present invention.

 The DNAs of the present invention include all DNAs coding

for the above-mentioned proteins. Said DNAs can be obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries of the human cell origin. These cDNA are synthesized by using as templates poly(A)⁺ RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the culture cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available, human cDNA libraries can be utilized. Cloning of the cDNAs of the present invention from the cDNA libraries can be carried out by synthesis of an oligonucleotide on the basis of an optional portion in the cDNA base sequences of the present invention, followed by screening using this oligonucleotide as the probe according to the colony or plaque hybridization by a method known in the art. In addition, the cDNA fragments of the present invention can be prepared by synthesis of an oligonucleotide to be hybridized at both termini of the objective cDNA fragment, followed by the usage of this oligonucleotide as the primer for the RT-PCR method from an mRNA isolated from human cells.

The cDNAs of the present invention are characterized by containing either of the base sequences represented by Sequence Nos. 10 to 18 or the base sequences represented by Sequence Nos. 19, 21, 23, 25, 27, 29, 31, 33 and 35. Table 1 summarizes the

clone number (HP number), the cells affording the cDNA, the total base number of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

5

Table 1

| Sequence No. | HP No. | Cell | Number of bases | Number of amino acids |
|--------------|---------|----------------|-----------------|-----------------------|
| 1, 10, 19 | HP02000 | Liver | 1705 | 268 |
| 2, 11, 20 | HP02061 | Saos-2 | 1759 | 236 |
| 3, 12, 21 | HP02163 | Saos-2 | 1069 | 261 |
| 4, 13, 22 | HP02219 | Stomach Cancer | 1759 | 328 |
| 5, 14, 23 | HP02256 | Stomach Cancer | 1697 | 300 |
| 6, 15, 24 | HP10390 | Stomach Cancer | 814 | 182 |
| 7, 16, 25 | HP10474 | Saos-2 | 511 | 66 |
| 8, 17, 26 | HP10527 | Saos-2 | 1126 | 183 |
| 9, 18, 27 | HP10528 | Saos-2 | 2015 | 324 |

Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines and human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of Sequence Nos. 10 to 19, 21, 23, 25, 27, 29, 31, 33 and 35.

In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA that is subjected to insertion or deletion of one or plural nucleotides and/or substitution with other nucleotides in Sequence Nos. 10 to 19, 21, 23, 25, 27, 29, 31, 33 and 35 shall come within the scope of the present invention.

In a similar manner, any protein that is formed by these modifications comprising insertion or deletion of one or plural amino acids and/or substitution with other amino acids shall

come within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by Sequence Nos. 1 to 9.

The cDNAs of the present invention include cDNA fragments
5 (more than 10 bp) containing any partial base sequence in the base sequences represented by Sequence Nos. 10 to 18 or in the base sequences represented by Sequence Nos. 19, 21, 23, 25, 27, 29, 31, 33 and 35. Also, DNA fragments consisting of a sense chain and an anti-sense chain shall come within this scope.
10 These DNA fragments can be utilized as the probes for the gene diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities
15 (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies
20 or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for
25 analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome
30 markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders;

as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response.

Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions

can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one

or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without
5 limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among
10 other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and
15 Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991;
20 Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation,
25 Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8,
30 John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without

limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may

also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a

peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells

that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms.

5 Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking

10 reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases.

15 Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

20

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing

25 immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the commoncold, and encephalitis might be alleviated

30 by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be

enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro
5 activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described
10 herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

15 In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least
20 one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression
25 vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell.
30 Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention

having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which
5 lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or
10 an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T
15 cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte
20 antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among
25 other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing
30 Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA

78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA
5 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991;
10 Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those
15 described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

20 Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W
25 Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol.
30 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that

activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of

factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in
5 treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity)
10 useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and
15 generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell
20 disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow
25 transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

30 Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which

will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lymphohematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the

treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament

tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders,

such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

5 Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

10 It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular
15 endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

20 A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

25 A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

30 Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon);

International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without
5 limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

10 A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of
15 follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration
20 of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in
25 stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such
30 as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays

that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-

inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by
5 inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can
10 be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or
15 chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an
20 antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A
25 protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting
30 angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing,

eliminating or inhibiting factors, agents or cell types which promote tumor growth

Other Activities

A protein of the invention may also exhibit one or more
5 of the following additional activities or effects: inhibiting
the growth, infection or function of, or killing, infectious
agents, including, without limitation, bacteria, viruses, fungi
and other parasites; effecting (suppressing or enhancing)
bodily characteristics, including, without limitation, height,
10 weight, hair color, eye color, skin, fat to lean ratio or other
tissue pigmentation, or organ or body part size or shape (such
as, for example, breast augmentation or diminution, change in
bone form or shape); effecting biorhythms or circadian cycles
or rhythms; effecting the fertility of male or female subjects;
15 effecting the metabolism, catabolism, anabolism, processing,
utilization, storage or elimination of dietary fat, lipid,
protein, carbohydrate, vitamins, minerals, cofactors or other
nutritional factors or component(s); effecting behavioral
characteristics, including, without limitation, appetite,
20 libido, stress, cognition (including cognitive disorders),
depression (including depressive disorders) and violent
behaviors; providing analgesic effects or other pain reducing
effects; promoting differentiation and growth of embryonic stem
cells in lineages other than hematopoietic lineages; hormonal
25 or endocrine activity; in the case of enzymes, correcting
deficiencies of the enzyme and treating deficiency-related
diseases; treatment of hyperproliferative disorders (such as,
for example, psoriasis); immunoglobulin-like activity (such as,
for example, the ability to bind antigens or complement); and
30 the ability to act as an antigen in a vaccine composition to
raise an immune response against such protein or another

material or entity which is cross-reactive with such protein.

Examples

The present invention is embodied in more detail by the following examples, but this embodiment is not intended to restrict the present invention. The basic operations and the enzyme reactions with regard to the DNA recombination are carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from TAKARA SHUZO. The manufacturer's instructions were used for the buffer compositions as well as for the reaction conditions, in each of the enzyme reactions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Preparation of Poly(A)⁺ RNA

The osteosarcoma cell line Saos-2 (ATCC HTB 85), tissues of stomach cancer delivered by the operation, and the liver were used for human cells to extract mRNAs. The cell line was incubated by a conventional procedure.

After about 1 g of the human cells was homogenized in 20 ml of a 5.5 M guanidinium thiocyanate solution, a total mRNA was prepared according to the literature [Okayama, H. et al., "Method in Enzymology", Vol. 164, Academic Press, 1987]. This was subjected to chromatography on oligo(dT)-cellulose column washed with a 20 mM Tris-hydrochloride buffer solution (pH 7.6), 0.5 M NaCl, and 1 mM EDTA to obtain a poly(A)⁺ RNA according to the above-described literature.

(2) Construction of cDNA Library

Ten micrograms of the above-mentioned poly(A)⁺ RNA were

dissolved in a 100 mM Tris-hydrochloride buffer solution (pH 8), one unit of an RNase-free, bacterial alkaline phosphatase was added, and the reaction was run at 37°C for one hour. After the reaction solution was subjected to phenol extraction, followed
5 by ethanol precipitation, the resulting pellet was dissolved in a solution containing 50 mM sodium acetate (pH 6), 1 mM EDTA, 0.1% 2-mercaptoethanol, and 0.01% Triton X-100. Thereto was added one unit of a tobacco-origin acid pyrophosphatase (Epicentre Technologies) and a total 100 μ l volume of the
10 resulting mixture was reacted at 37°C for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in water to obtain a solution of a decapped poly(A)⁺ RNA.

The decapped poly(A)⁺ RNA and 3 nmol of a chimeric DNA-RNA
15 oligonucleotide (5'-dG-dG-dG-dG-dA-dA-dT-dT-dC-dG-dA-G-G-A-3') were dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 7.5), 0.5 mM ATP, 5 mM MgCl₂, 10 mM 2-mercaptoethanol, and 25% polyethylene glycol, whereto was added 50 units of T4RNA ligase and a total 30 μ l volume of
20 the resulting mixture was reacted at 20°C for 12 hours. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in water to obtain a chimeric-oligo-capped poly(A)⁺ RNA.

25 After digestion of vector pKA1 (Japanese Patent Kokai Publication No. 1992-117292) developed by the present inventors with KpnI, about 60 dT tails were added using a terminal transferase. A vector primer to be used below was prepared by digestion of this product with EcoRV to remove a dT tail at one
30 side.

After 6 μ g of the previously-prepared chimeric-oligo-capped poly(A)⁺ RNA was annealed with 1.2 μ g of the vector

primer, the resulting product was dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 8.3), 75 mM KCl, 3 mM MgCl₂, 10 mM dithiothreitol, and 1.25 mM dNTP (dATP + dCTP + dGTP + dTTP), 200 units of a reverse transcriptase (GIBCO-BRL) were added, and the reaction in a total 20 µl volume was run at 42°C for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 50 mM Tris-hydrochloride buffer solution (pH 7.5), 100 mM NaCl, 10 mM MgCl₂, and 1 mM dithiothreitol. Thereto were added 100 units of EcoRI and a total 20 µl volume of the resulting mixture was reacted at 37°C for one hour. After the reaction solution was subjected to phenol extraction, followed by ethanol precipitation, the resulting pellet was dissolved in a solution containing 20 mM Tris-hydrochloride buffer solution (pH 7.5), 100 mM KCl, 4 mM MgCl₂, 10 mM (NH₄)₂SO₄, and 50 µg/ml of the bovine serum albumin. Thereto were added 60 units of an *Escherichia coli* DNA ligase and the resulting mixture was reacted at 16°C for 16 hours. To the reaction solution were added 2 µl of 2 mM dNTP, 4 units of *Escherichia coli* DNA polymerase I, and 0.1 unit of *Escherichia coli* RNase H and the resulting mixture was reacted at 12°C for one hour and then at 22°C for one hour.

Next, the cDNA-synthesis reaction solution was used for transformation of *Escherichia coli* DH12S (GIBCO-BRL). The transformation was carried out by the electroporation method. A portion of the transformant was sprayed on the 2xYT agar culture medium containing 100 µg/ml ampicillin and the mixture was incubated at 37°C overnight. A colony formed on the agar medium was picked up at random and inoculated on 2 ml of the 2xYT culture medium containing 100 µg/ml ampicillin. After incubation at 37°C overnight, the culture mixture was

centrifuged to separate the mycelia, from which a plasmid DNA was prepared by the alkaline lysis method. The plasmid DNA was subjected to double digestion with EcoRI and NotI, followed by 0.8% agarose gel electrophoresis, to determine the size of the
5 cDNA insert. Furthermore, using the thus-obtained plasmid as a template, the sequence reaction was carried out by using an M13 universal primer labeled with a fluorescent dye and a Taq polymerase (a kit of Applied Biosystems) and then the product was examined with a fluorescent DNA sequencer (Applied
10 Biosystems) to determine an about 400-bp base sequence at the 5'-terminus of the cDNA. The sequence data were filed as the homo/protein cDNA bank database.

(3) Selection of cDNAs Encoding Proteins Having Transmembrane Domains

15 A base sequence registered in the homo/protein cDNA bank was converted to three frames of amino acid sequences and the presence or absence of an open reading frame (ORF) beginning from the initiation codon was examined. Then, the selection was made for the presence of a signal sequence that is
20 characteristic to a secretory protein at the N-terminus of the portion encoded by the ORF. These clones were sequenced from the both 5' and 3' directions by the use of the deletion method using exonuclease III to determine the whole base sequence. The hydrophobicity/hydrophilicity profiles were obtained for
25 proteins encoded by the ORF by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. In the case in which there is a hydrophobic region of a putative transmembrane domain in the amino acid sequence of an encoded
30 protein, this protein was judged as a membrane protein.

(4) Functional Verification of Secretory Signal Sequence or Transmembrane Domains

It was verified by the method described in the literature [Yokoyama-Kobayashi, M. et al., Gene 163: 193-196 (1995)] that the N-terminal hydrophobic region in the secretory protein clone candidate obtained in the above-mentioned steps functions as a secretory signal sequence. First, the plasmid containing the target cDNA was cleaved at an appropriate restriction enzyme site existing at the downstream of the portion expected for encoding the secretory signal sequence. In the case in which this restriction site was a protruding terminus, the site was blunt-ended by the Klenow treatment or treatment with the T4DNA polymerase. Digestion with HindIII was further carried out and a DNA fragment containing the SV40 promoter and a cDNA encoding the secretory signal sequence at the downstream of the promoter was separated by agarose gel electrophoresis. The resulting fragment was inserted between HindIII in pSSD3 (DDBJ/EMBL/GenBank Registration No. AB007632) and a restriction enzyme site selected so as to match with the urokinase-coding frame, thereby constructing a vector expressing a fusion protein of the secretory signal sequence of the target cDNA and the urokinase protease domain.

After *Escherichia coli* (host: JM109) bearing the fusion-protein expression vector was incubated at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing 100 µg/ml of ampicillin, the helper phage M13K07 (50 µl) was added and the incubation was continued at 37°C overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles were suspended in 100 µl of 1 mM Tris-0.1 mM EDTA, pH 8 (TE). Also, there were used as controls suspensions of single-stranded phage particles prepared in the same manner from pSSD3 and from the vector pKAl-UPA containing a full-length cDNA of urokinase [Yokoyama-Kobayashi, M. et al., Gene

163: 193-196 (1995)].

The culture cells originating from the simian kidney, COS7, were incubated at 37°C in the presence of 5% CO₂ in the Dulbecco's modified Eagle's culture medium (DMEM) containing
5 10% fetal calf albumin. Into a 6-well plate (Nunc Inc., 3 cm in the well diameter) were inoculated 1×10^5 COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO₂. After the culture medium was removed, the cell surface was washed with a phosphate buffer solution and then
10 washed again with DMEM containing 50 mM Tris-hydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 µl of the single-stranded phage suspension, 0.6 ml of the DMEM culture medium, and 3 µl of TRANSFECTAM (IBF Inc.) and the resulting mixture was incubated at 37°C for 3 hours in the
15 presence of 5% CO₂. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf albumin was added, and the incubation was carried out at 37°C for 2 days in the presence of 5% CO₂.

To 10 ml of 50 mM phosphate buffer solution (pH 7.4)
20 containing 2% bovine fibrinogen (Miles Inc.), 0.5% agarose, and 1 mM calcium chloride were added 10 units of human thrombin (Mochida Pharmaceutical Co., Ltd.) and the resulting mixture was solidified in a plate of 9 cm in diameter to prepare a fibrin plate. Ten microliters of the culture supernatant of the
25 tansfected COS7 cells were spotted on the fibrin plate, which was incubated at 37°C for 15 hours. In the case in which a clear circle appears on the fibrin plate, it is judged that the cDNA fragment codes for the amino acid sequence functioning as a secretory signal sequence. On the other hand, in case in
30 which a clear circle is not formed, the cells were washed well, then the fibrin sheet was plac d on the cells, and incubation was carried out at 37°C for 15 hours. In case in which a clear

portion is formed on the fibrin sheet, it indicates that the urokinase activity was expressed on the cell surface. In other words, the cDNA fragment is judged to code for the transmembrane domains.

5 (5) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [³⁵S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was reacted at 30°C for 90 minutes in a total 25 µl volume of the reaction solution containing 12.5 µl of T_NT rabbit reticulocyte lysate, 0.5 µl of a buffer solution
10 (attached to kit), 2 µl of an amino acid mixture (methionine-free), 2 µl of [³⁵S]methionine (Amersham) (0.37 MBq/µl), 0.5 µl of T7RNA polymerase, and 20 U of RNasin. To 3 µl of the resulting reaction solution was added 2 µl of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and
15 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

25 (6) Expression by COS7

Escherichia coli bearing the expression vector of the protein of the present invention was infected with helper phage M13K07 and single-stranded phage particles were obtained by the above-mentioned procedure. The thus-obtained phage was used for
30 introducing each expression vector in the culture cells originating from the simian kidney, COS7. After incubation at 37°C for 2 days in the presence of 5% CO₂, the incubation was

continued for one hour in the culture medium containing [³⁵S]cystine or [³⁵S]methionine. Collection and dissolution of the cells, followed by subjecting to SDS-PAGE, allowed to observe the presence of a band corresponding to the expression product of each protein, which did not exist in the COS7 cells.

(7) Northern Blot Hybridization

Northern blot hybridization was carried out in order to examine the expression pattern in the human tissues. Filters where poly(A)⁺ RNAs isolated from each of human tissues are blotted were purchased from Clontech. After excision of a cDNA fragment from the objective clone, followed by agarose-gel electrophoresis to isolate the cDNA fragment, labeling with [³²P]dCTP (Amersham) was carried out by using a random primer labeling kit (TAKARA SHUZO). The hybridization was carried out by using a solution attached to the blot paper according to the protocol.

(8) Clone Examples

<HP02000> (Sequence Nos. 1, 10, and 19)

Determination of the whole base sequence of the cDNA insert of clone HP02000 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 186-bp 5'-nontranslation region, an 807-bp ORF, and a 712-bp 3'-nontranslation region. The ORF codes for a protein consisting of 268 amino acid residues and there existed two putative transmembrane domains. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was almost identical with the molecular weight of 30,481 predicted from the ORF. When expressed in COS 7 cells, an expression product of about 32 kDa was observed in the membrane fraction.

The search of the protein data base by using the amino acid sequence of the present protein revealed that the protein was analogous to the rat organic cation transporter (EMBL Accession No. Y09945). Table 2 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the rat organic cation transporter (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 67.5% in the N-terminal 169 amino acid residues.

Table 2

| | |
|----|--|
| 15 | <hr/> HS MAFEELLSQVGGGLGRFQMLHLVFIPLSIMLLIPHILLENFAAAIPGHRWCWHMLDNNTGS ***..**.*..*****.*...*** ... ** ..**.*..**.*..*****..**.* * RN MAFQDLLNQVGSGLGRFQILQMTFILIFNIIISPHSLLENFTAVIPNHRWCWPILDNDTVS HS GNETGILSEDALLRISIPLDSNLRPEKCRRFVHPQWQLLHLNGTIHSTSEADTEPCVDGW **..* **.*..**.*..*****..*****..**.*..*****. *..*..***** RN GNDNGNLSQDDLLRVSIPLDSNLRPEKCRRFVQWQWDLHLNGTFSSVTEPDTEPCVDGW HS VYDQSYFPSTIVTKWDLVCDYQSLKSVVQFLLLTGMLVGGIIGGHVSDRWLVESARWLII ***** * ..**.*..*****. ***.*...**.*..**.*..**.*. *...** RN VYDQSTFLSTIITEWDLVCESQSLDSIAKFLFTGILVGNILYGPLTDRFGRRLLILCAS HS TNKLDEGLKALRKVARTNGIKNAEETLNIEVVRSTMQEELDAAQTKTIVCDLFRNPSMRK RN LQMAVTETCAAFAPTFLIYCSLRFAGISFSTVLNLSALLIIIEWTRPKFQALATGLLLCA HS RICILVFLRKKISRKRHKNDCTYTKVTKF RN GAIGQTVLAGLAFTVRNWHHLHLAMSVPIFFLLVPTRWLSesarwLIMTNKLQKGLKELI <hr/> |
| 20 | |
| 25 | |
| 30 | |

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. AA680184) in EST, but any of the sequences was shorter than the present cDNAs and was not found to contain the initiation codon.

An investigation of the expression pattern in the tissues by northern blot hybridization using the cDNA fragment of the present invention has revealed the expression only in the liver.

The rat organic cation transporter has been found as a membrane protein associated with a drug excretion in the kidney [Grundemann, D. et al., Nature 372: 549-552 (1994)]. Accordingly, the protein of the present invention that is its homologue is considered to possess a similar function and can be utilized for the diagnosis and treatment of diseases that are associated with abnormalities of this enzyme. Furthermore, this is considered to be associated with a drug excretion, so that the cells expressing this protein can be used as a tool for designing this drug. In addition, since this protein is expressed specifically in the liver, a substance prepared so as to possess an affinity with this protein can be applied to the drug delivery system to the liver.

<HP02061> (Sequence Nos. 2, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP02061 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 141-bp 5'-nontranslation region, a 711-bp ORF, and a 907-bp 3'-nontranslation region. The ORF codes for a protein consisting of 236 amino acid residues and there existed two putative transmembrane domains. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation

Table 3

```

20      HS MAEPSAATQSHSISSSSFGAEPSAPGGGGSPGACPALGTKSCSSSCAVHDLIFWRDVKQT
                                                ***.***.*.*
PC      MQATADSTKMDCVWSNWKSQAIDLLYWRDIKQT
HS      GFVFGTTLIMLLSLAAFSVISVVSYLILALLSVTISFRIYKSVIQAVQKSEEGHPFKAYL
        *.***. *..*.*.*.***.***.*.* ** *.*****.*****.*****.*****
PC      GIVFGSFLLLLFSLTQFSVVSVVAYLALAALSATISFRIYKSVLQAVQKTEDEGHPFKAYL
25      HS DVDITLSSEAFHNYMNAAMVHINRALKLIIRLFLVEDLVDSLKLAVFMWMLTYVGAVFNG
        ...**** *...* .    ..*.*.* . *****.*****.*.*.***.*****.***
PC      ELEITLSQEIQKYTDCLQFYVNSTLKELRRLFLVQDLVDSLKFVILMWLLTYVGALFNG
HS      ITLLILAEELLIFSVPYVYKYKTQIDHYVGIARDQTKSIVEKIQAKLPGIAKKKAE
        ***.*.* . *..*.*.* *...***.*.*.*.....*.*****.*.* **.*.*
30      PC LTLLMAVVSMTFLPVVYVKHOAOIDOYVGLVRTHINAVVAKIQAKIPG-AKRHAE

```

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. AA362885) in EST, but, since they are partial
5 sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02163> (Sequence Nos. 3, 12, and 23)

Determination of the whole base sequence of the cDNA
10 insert of clone HP02163 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 179-bp 5'-nontranslation region, a 786-bp ORF, and a 104-bp 3'-nontranslation region. The ORF codes for a protein consisting of 261 amino acid residues and there existed one
15 putative transmembrane domain. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was almost identical with the molecular weight of 29,932
20 predicted from the ORF. When expressed in COS 7 cells, an expression product of about 28 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed the presence of
25 sequences that were analogous to a yeast hypothetical protein of 29.4 kDa (SWISS-PROT Accession No. P36039). Table 4 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the yeast hypothetical protein of 29.4 kDa (SC). Therein, the marks of -,
30 *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively.

The both proteins possessed a homology of 33.2% in the entire region.

Table 4

5

```

HS          MAGPELLLDSNIRLWVVLPIVIITFFVGMIRHYVSI
          .*.*****. ***.*** *. .*.*****. .
SC MTINQHLQQLLFNRIDKTTSSIQQARAPQMLDDQLKYWVLLPISIVMVLTGVLKQYIMT
HS LL---QSDKKLQEQVSDSQVLIRSRVIRENGKYIPKQSFLTRK-YYFNN-PEDGFFKKT
10  *.    ... .. .... * * .....* .** .....* ..* . .. *. . *.
SC LITGSSANEAQPRVKLTEWQYLQWAQLLIGNGGLSSDAFAAKKEFLVKDLTEERHLAKA
HS KRK-----VVPSPMTDPTM---LTDMMKGNVTNVLPILIGGWINMTFSGFVITKVPFP
          *..          *.*****. . *.*****. *.** *.** *.***. ....
SC KQDGSQAGEVPNPFNDPSMSNAMNMAKGNMASFIPQTIIMWWVNHFFAGFILMQLPFP
15  H3 LTLRFKPMLOQGIELLTLDSWSSASWYFLNVFGLRSIYSLI-LGQDNAADQSRMMQEQ
          ** .** *** ** .***.***** *****.*****.*** *.... . *.
SC LTAKFKEMLQTGIICQDLVVRWSSISWYFISVLGLNPVYNLIGLNDQDMGIQAGIGGPQ
HS MTGAAMAMPADTNKAFKTEWEALELTDHQWALDDVEEELMAKDLHFEGMFKKELQTSIF
20  SC APKALHNHRLTKQCMRWLTI

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. Z43161) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

30 <HP02219> (Sequence Nos. 4, 13, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP02219 obtained from cDNA libraries of human

stomach cancer revealed the structure consisting of a 58-bp 5'-nontranslation region, a 987-bp ORF, and a 714-bp 3'-nontranslation region. The ORF codes for a protein consisting of 328 amino acid residues and there existed one putative transmembrane domain. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 39 kDa that was almost identical with the molecular weight of 37,299 predicted from the ORF. When expressed in COS 7 cells, an expression product of about 39 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to *Alabidopsis thaliana* dTDP-glucose 4-6-dehydratase homologue (PIR Accession No. S58282). Table 5 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the *Alabidopsis thaliana* dTDP-glucose 4-6-dehydratase homologue (AT). Therein, the marks of * and . represent an amino acid residue identical with the protein of the present invention and an amino acid residue analogous to the protein of the present invention, respectively. The both proteins possessed a homology of 57.2% in 145 amino acid residues at the C-terminal region.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, 25 Accession No. U46355) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. U46355) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02256> (Sequence Nos. 5, 14, and 27)

Determination of the whole base sequence of the cDNA insert of clone HP02256 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 131-bp 5'-nontranslation region, a 903-bp ORF, and a 663-bp 3'-nontranslation region. The ORF codes for a protein consisting of 300 amino acid residues and there existed one transmembrane domain at the N-terminus. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 33 kDa that was almost identical with the molecular weight of 32,943 predicted from the ORF. When expressed in COS cells, an expression product of about 30 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was analogous to the *Caenorhabditis elegans* hypothetical protein T11F9.11 (PID Accession No. 1403260). Table 6 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the *Caenorhabditis elegans* hypothetical protein T11F9.11 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with the protein of the present invention, and an amino acid residue analogous to the protein of the present invention, respectively.

The both proteins possessed a homology of 41.7% in the entire region.

Table 6

5

HS MKFLLDIILLPLLVCSLESFVKLFIPK---RRKSVTGEIVLITGAGHGIGRLTAYEFA

 **.. . . . * * * * * * * * . * * * * *

CE MDRALDFVKMVGTLFFIVLNFFKNFLPNGVLPKRSVEGKKVLITGSGSGIGRLMALEFA

HS KLKSKLVLDINKHGLEETAACKCKGLGAKVHTFVVDCSNREDIYSSAKKVKAIEIGDVSIL

10

 ** ..*.*.*.* * * * .. * . * . * * * * . * * . . * * . . . * * *

CE KLGAEVVIWDVKNKGAEETKNQVVKAGGKASTFVVDLSQYKDIHKVAKETKEAVGDIDIL

HS VNNAGVVYTSDLFATQDPQIEKTFEVNVLAHFWITKAFLPAMTKNNHGHIVTVASAAGHV

 * * * * . * * * . * . * * * . * * * . * * * . * * * . * * * . * * *

CE INNAGIVTGKKLFDCPDELMEKTMVNTNALFYTAKNFLPSMLEKDNHGLVTIASMAGKT

15

HS SVPFLLAYCSSKFAAVGFHKTLTDELAALQITGVKTTCLCPNFVNTG-F--IKNPSTSLG

 . * * * * . * * * * . * * . * * * * . * * * * . * * * * . * * *

CE GCVGLVDYCASKHGAIGCHDSIAMEILAQKKYGVNTTLVCPFFIDTGMFHVTTKCPALF

HS PTLPEEVVNRIMHGILTEQKMIFIPSSIAFLTTLERILPERFLAVLKRKISVKFDAVIG

 * . * * . * * * * . . . * * . . . * * . * *

20

CE PILEANYAVECIVEAILTNRPLLMPKASYLILALIGLLPIESQVMMADFFGTNESMNDF

HS YKMQAQ

CE KGRQKND

25

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that possessed a homology of 90% or more (for example, Accession No. H61494) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the

30

present invention.

<HP10390> (Sequence Nos. 6, 15, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10390 obtained from cDNA libraries of human stomach cancer revealed the structure consisting of a 144-bp 5'-nontranslation region, a 549-bp ORF, and a 121-bp 3'-nontranslation region. The ORF codes for a protein consisting of 182 amino acid residues and possessed one transmembrane domain in the N-terminus. Figure 6 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Introduction of an expression vector, wherein the HindIII-BstXI (treated with T4RNA polymerase) fragment containing a cDNA portion coding for the N-terminal 50 amino acid residues of the present protein was inserted into the HindIII-SmaI site of pSSD3, into the COS7 cells revealed the urokinase activity on the surface of the cells to indicate that the present protein is the type-II membrane protein. In vitro translation resulted in formation of a translation product of 20 kDa that was almost identical with the molecular weight of 20,639 predicted from the ORF. When expressed in COS cells, an expression product of about 19 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has not identified any known protein having an analogy. Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. AA315322) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10474> (Sequence Nos. 7, 16, and 31)

Determination of the whole base sequence of the cDNA insert of clone HP10474 obtained from cDNA libraries of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 22-bp 5'-nontranslation region, a 201-bp ORF, and a 288-bp 3'-nontranslation region. The ORF codes for a protein consisting of 66 amino acid residues and possessed one transmembrane domain at the C-terminus. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 7,599 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. H30340) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10527> (Sequence Nos. 8, 17, and 33)

Determination of the whole base sequence of the cDNA insert of clone HP10527 obtained from cDNA libraries of the human osteosarcoma cell line Saos-2 revealed the structure consisting of a 113-bp 5'-nontranslation region, a 552-bp ORF, and a 461-bp 3'-nontranslation region. The ORF codes for a protein consisting of 183 amino acid residues and possessed three putative transmembrane domains. Figure 8 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. As the result of in

vitro translation, there was produced a translation product of about 21 kDa, which is nearly equal to a molecular weight of 21,111 as expected from ORF.

The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of 90% or more (for example, Accession No. AA310892) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10528> (Sequence Nos. 9, 18, and 35)

Determination of the whole base sequence of the cDNA insert of clone HP10528 obtained from cDNA libraries of the human osteosarcoma cell line Saos-2 revealed the structure consisting of a 53-bp 5'-nontranslation region, a 975-bp ORF, and a 987-bp 3'-nontranslation region. The ORF codes for a protein consisting of 324 amino acid residues and possessed seven putative transmembrane domains. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. As the result of in vitro translation, there was produced a translation product of about 32 kDa, which is nearly equal to a molecular weight of 34,227 as expected from ORF.

The search of the protein data base using the amino acid sequence of the present protein has revealed it had an analogy to the epithelial cell growth arrest-inducible gene product (PID Accession No. 998569). Table 7 shows the comparison of the amino acid sequence between the human protein of the present invention (HP) and the epithelial cell growth arrest-inducible gene product (GA). Therein, the marks of -, *, and . represent

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The search of the protein data base using the amino acid sequence of the present protein has not revealed the presence of any known protein having an analogy. Also, the search of the GenBank using the base sequences of the present cDNA has revealed the presence of sequences that possessed a homology of

90% or more (for example, Accession No. AA206511) in EST, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

5

INDUSTRIAL APPLICABILITY

The present invention provides human proteins having transmembrane domains, cDNAs coding for these proteins, and expression vectors of said cDNAs as well as eucaryotic cells
10 expressing said cDNAs. All of the proteins of the present invention exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as
15 carcinostatic agents relating to the control of the proliferation and the differentiation of the cells or as antigens for preparing antibodies against said proteins. The cDNAs of the present invention can be utilized as probes for the gene diagnosis and gene sources for the gene therapy.
20 Furthermore, the cDNAs can be utilized for large-scale expression of said proteins. Cells, wherein these membrane protein genes are introduced to possess said proteins on the membrane surface, can be utilized for detection of the corresponding ligands, screening of novel low-molecular
25 pharmaceuticals, and so on.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide
30 sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited

to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): 250-254; Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially

or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at

least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides

disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably
5 highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and
10 reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table

| Stringency Condition | Polynucleotide Hybrid | Hybrid Length (bp) [‡] | Hybridization Temperature and Buffer [†] | Wash Temperature and Buffer [†] |
|----------------------|-----------------------|---------------------------------|---|--|
| A | DNA : DNA | ≥50 | 65°C; 1×SSC -or- 42°C; 1×SSC, 50% formamide | 65°C; 0.3×SSC |
| B | DNA : DNA | <50 | T _B *; 1×SSC | T _B *; 1×SSC |
| C | DNA : RNA | ≥50 | 67°C; 1×SSC -or- 45°C; 1×SSC, 50% formamide | 67°C; 0.3×SSC |
| D | DNA : RNA | <50 | T _D *; 1×SSC | T _D *; 1×SSC |
| E | RNA : RNA | ≥50 | 70°C; 1×SSC -or- 50°C; 1×SSC, 50% formamide | 70°C; 0.3×SSC |
| F | RNA : RNA | <50 | T _F *; 1×SSC | T _F *; 1×SSC |
| G | DNA : DNA | ≥50 | 65°C; 4×SSC -or- 42°C; 4×SSC, 50% formamide | 65°C; 1×SSC |
| H | DNA : DNA | <50 | T _H *; 4×SSC | T _H *; 4×SSC |
| I | DNA : RNA | ≥50 | 67°C; 4×SSC -or- 45°C; 4×SSC, 50% formamide | 67°C; 1×SSC |
| J | DNA : RNA | <50 | T _J *; 4×SSC | T _J *; 4×SSC |
| K | RNA : RNA | ≥50 | 70°C; 4×SSC -or- 50°C; 4×SSC, 50% formamide | 67°C; 1×SSC |
| L | RNA : RNA | <50 | T _L *; 2×SSC | T _L *; 2×SSC |
| M | DNA : DNA | ≥50 | 50°C; 4×SSC -or- 40°C; 6×SSC, 50% formamide | 50°C; 2×SSC |
| N | DNA : DNA | <50 | T _N *; 6×SSC | T _N *; 6×SSC |
| O | DNA : RNA | ≥50 | 55°C; 4×SSC -or- 42°C; 6×SSC, 50% formamide | 55°C; 2×SSC |
| P | DNA : RNA | <50 | T _P *; 6×SSC | T _P *; 6×SSC |
| Q | RNA : RNA | ≥50 | 60°C; 4×SSC -or- 45°C; 6×SSC, 50% formamide | 60°C; 2×SSC |
| R | RNA : RNA | <50 | T _R *; 4×SSC | T _R *; 4×SSC |

5

‡ : The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid

length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

† : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C)=81.5 + 16.6(log₁₀[Na⁺]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

CLAIMS

1. A protein comprising any of the amino acid sequences represented by Sequence Nos. 1 to 9.

5 2. A DNA coding for any of the proteins as claimed in Claim 1.

3. A cDNA comprising any of the base sequences represented by Sequence Nos. 10 to 18.

10 4. The cDNA as claimed in Claim 3 comprising any of the base sequences represented by Sequence Nos. 19, 21, 23, 25, 27, 29, 31, 33 and 35.

5. An expression vector capable of expressing the DNA as claimed in any of Claim 2 to Claim 4 by in vitro translation or in eucaryotic cells.

15 6. A transformation eucaryotic cell capable of expressing the DNA as claimed in any of Claim 2 to Claim 4 and producing the protein as claimed in Claim 1.

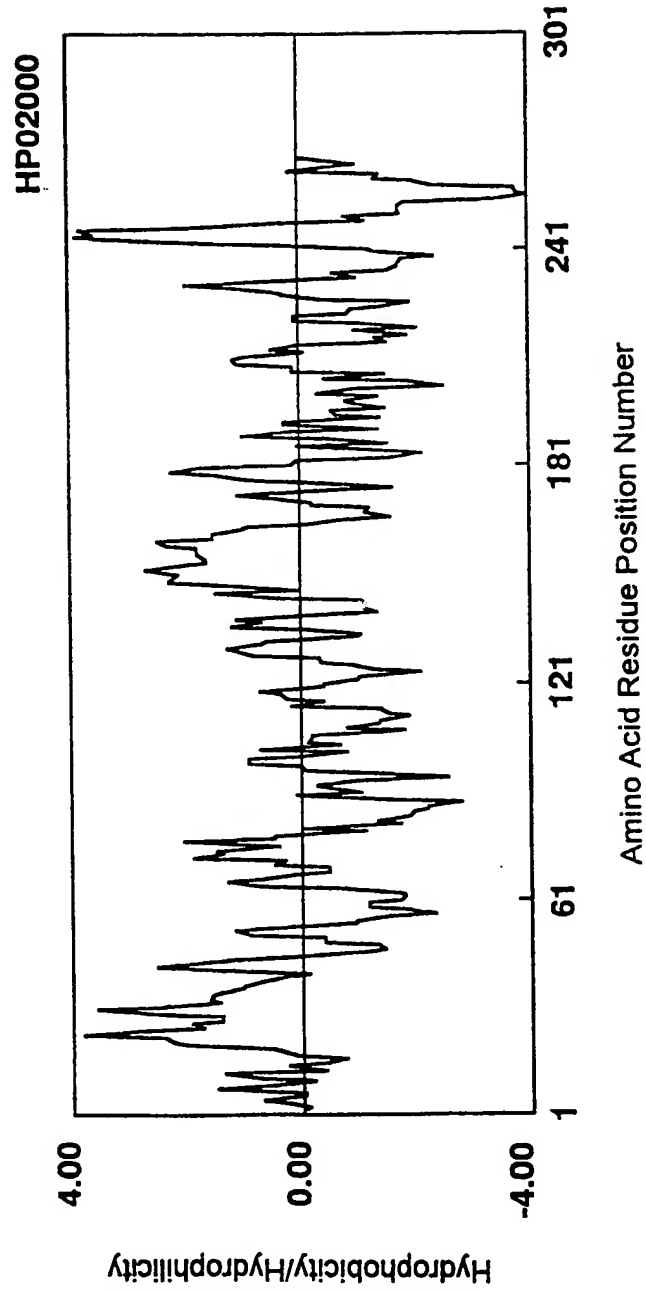


Fig. 1

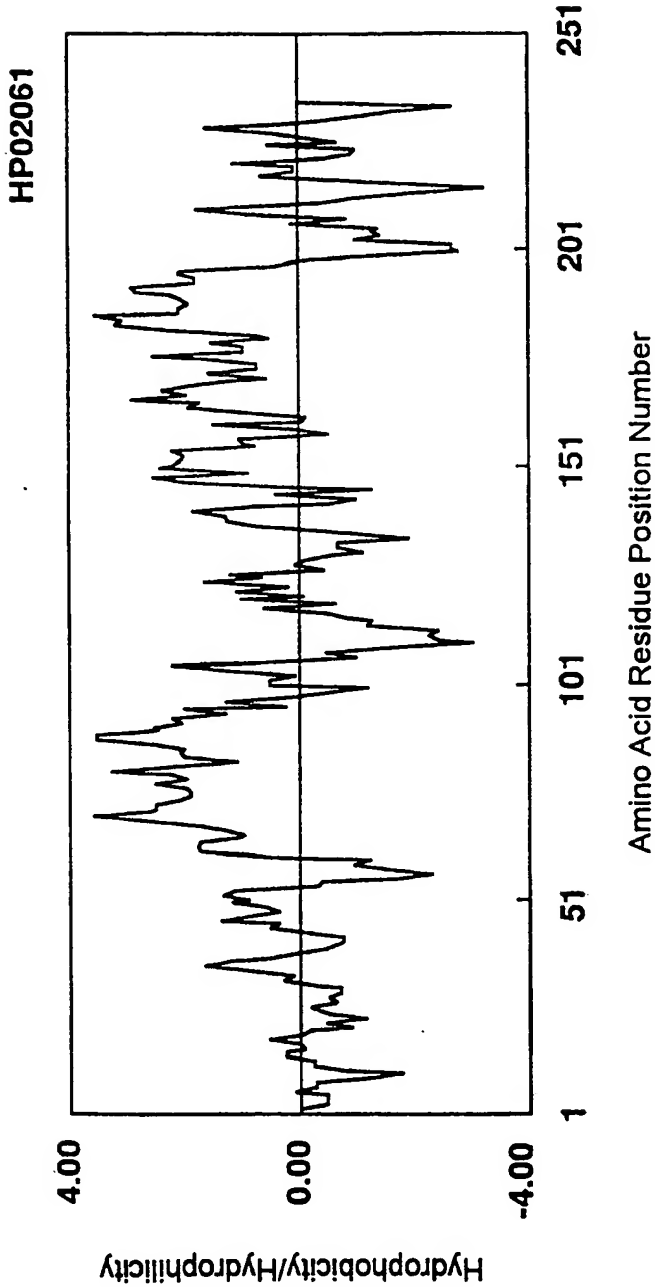


Fig. 2

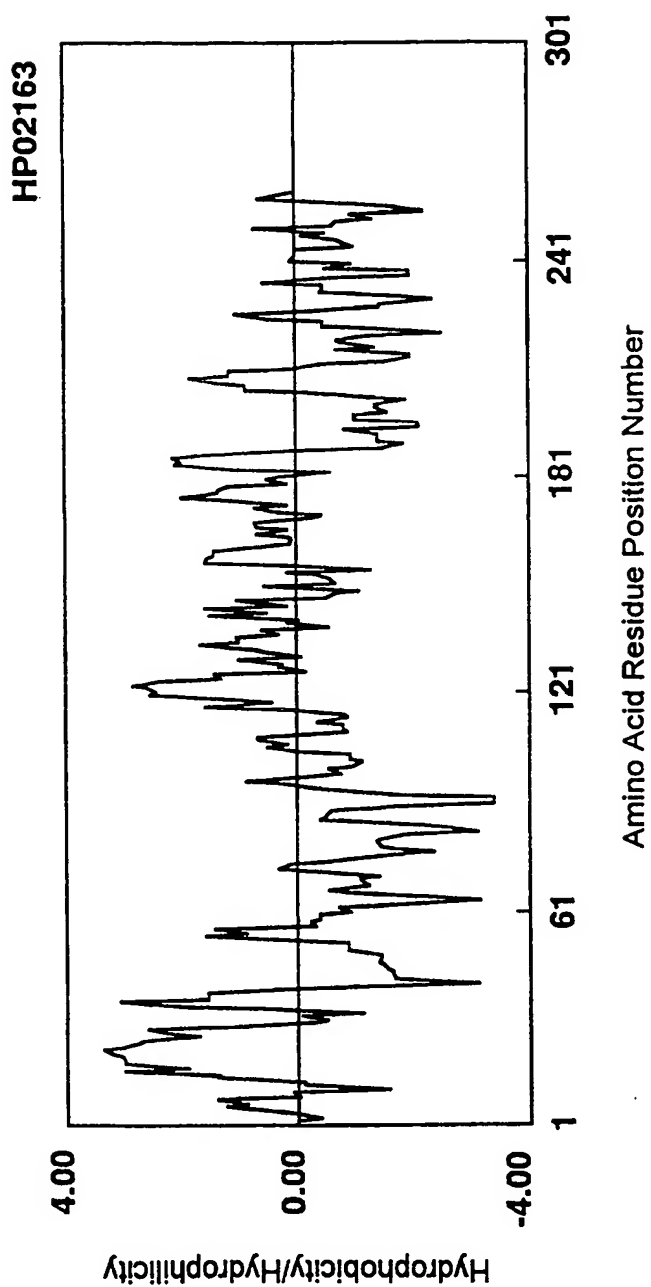


Fig. 3

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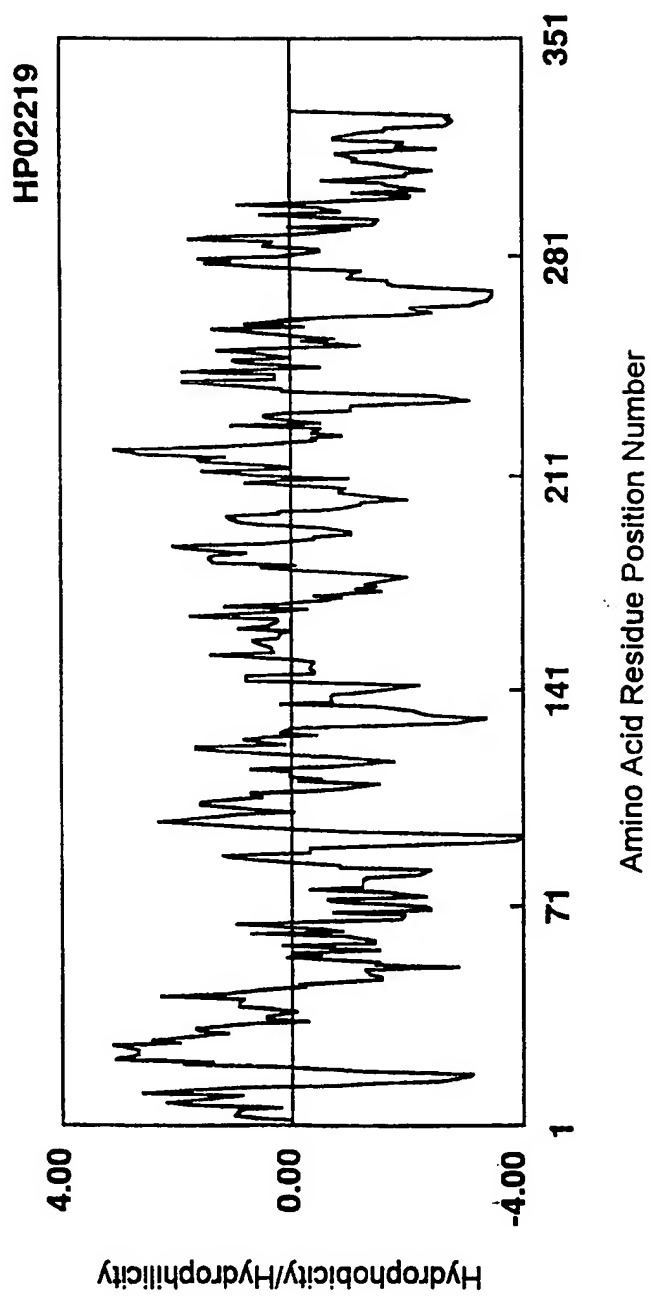


Fig. 4

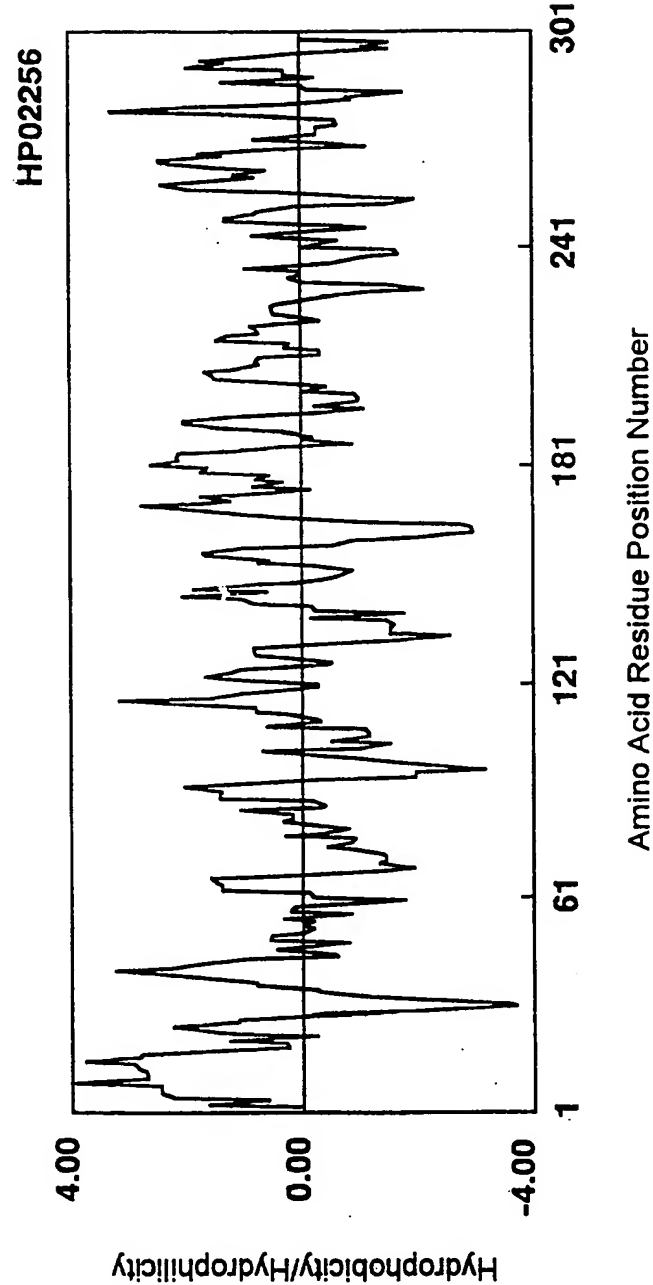


Fig. 5

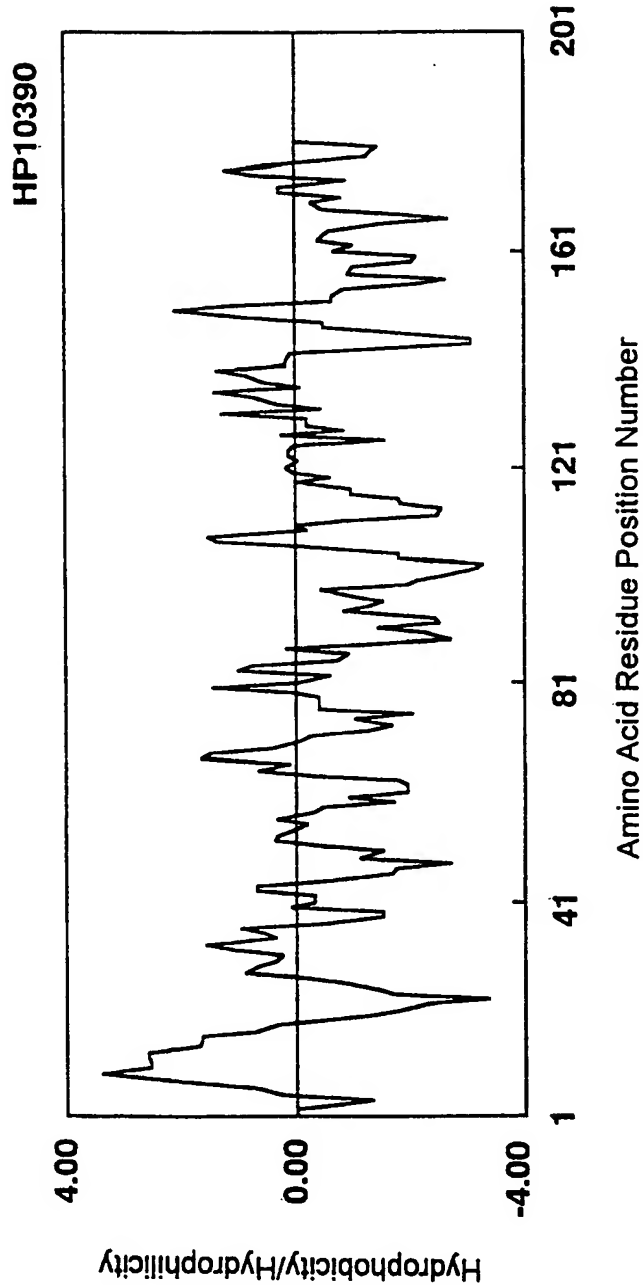


Fig. 6

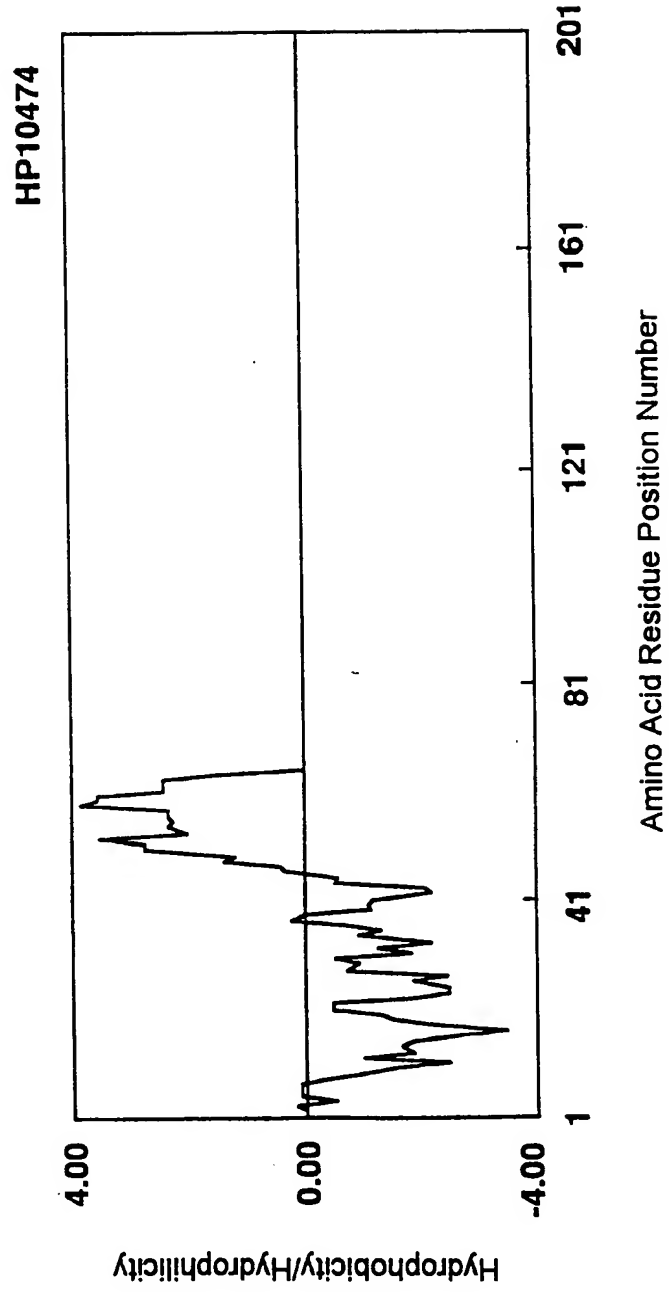


Fig. 7

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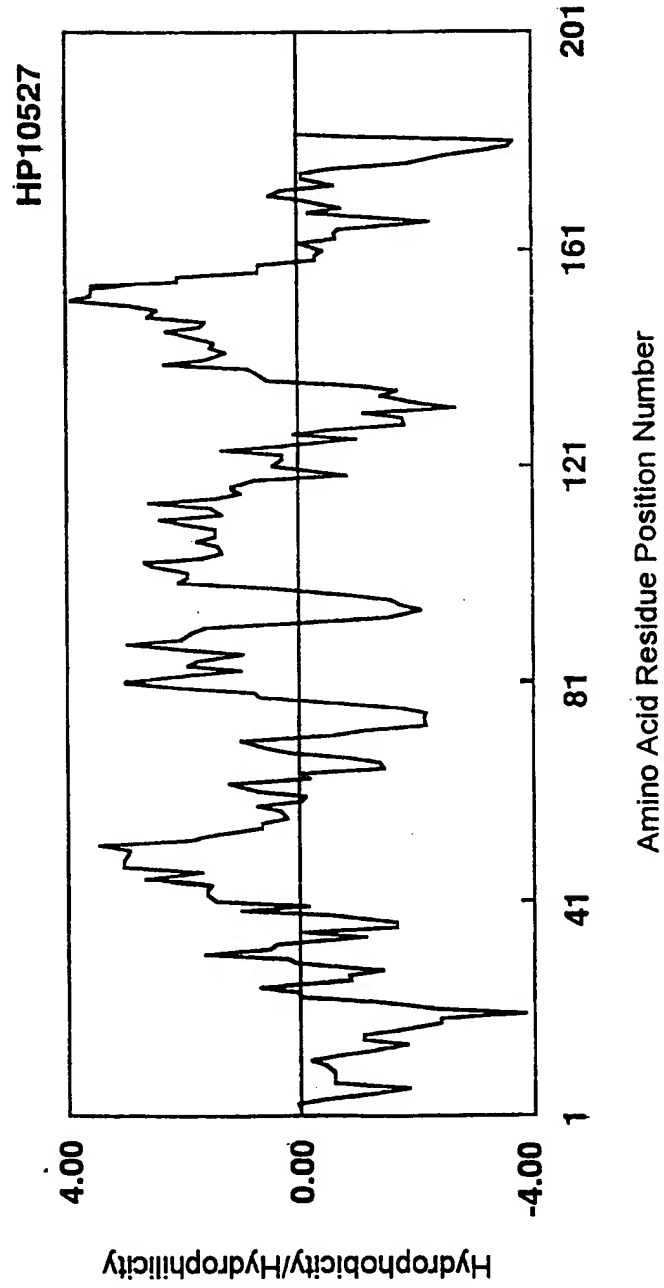


Fig. 8

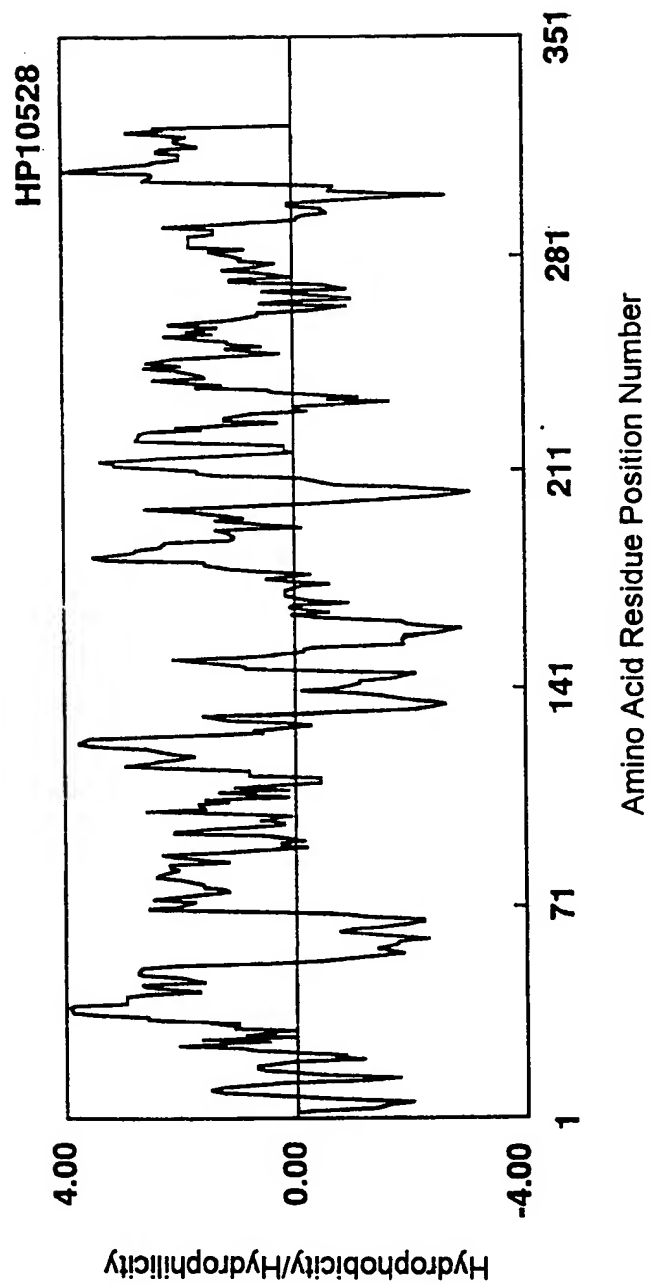


Fig. 9

Sequence listing

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Pro His Ile Leu Leu Glu Asn Phe Ala Ala Ala Ile Pro Gly His Arg

35 40 45

Cys Trp Val His Met Leu Asp Asn Asn Thr Gly Ser Gly Asn Glu Thr

50 55 60

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 85 90 95
 Gln Leu Leu His Leu Asn Gly Thr Ile His Ser Thr Ser Glu Ala Asp
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 Lys Val Ala Arg Thr Asn Gly Ile Lys Asn Ala Glu Glu Thr Leu Asn
 195 200 205
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Lys Tyr Pro Pro Val Lys Phe Leu Ser Glu Lys Asp Arg Lys Arg Ile
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11.

| | | |
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| | 290 295 300 | |
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| | ctggttttta ttcttccctc tctcatgtta ttaatccctc atatactgct agagaacttt | 120 |
| | gctgcagcca ttcctggtca tcgttgctgg gtccacatgc tggacaataa tactggatct | 180 |
| 20 | ggtaatgaaa ctggaatcct cagtgaagat gccctcttga gaatctctat cccactagac | 240 |
| | tcaaactctga ggccagagaa gtgtcgtcgc tttgtccatc ccagtgga gcttcttcac | 300 |
| | ctgaatggga ctatccacag cacaagtgag gcagacacag aaccctgtgt ggatggctgg | 360 |
| | gtatatgata aaagctactt cccttcgacc atttgtacta agtgggacct ggtatgtgat | 420 |
| | tatcagtcac tgaaatcagt ggttcaattc ctacttctga ctggaatgct ggtgggaggc | 480 |
| 25 | atcatagggtg gccatgtctc agacagggtg ctggtggaat ctgctcgggtg gttgataatc | 540 |
| | accaataaac tagatgaggg cttaaaggca cttagaaaag ttgcacgcac aaatggaata | 600 |
| | aagaatgctg aagaaaccct gaacatagag gttgtaagat ccaccatgca ggaggagctg | 660 |
| | gatgcagcac agacccaaac tactgtgtgt gacttggtcc gcaaccccag tatgcgtaaa | 720 |
| | aggatctgta tcctggtatt ttgagaaaa aaaatctcaa ggaaaaggca taaaaatgat | 780 |
| 30 | tgctacacaa aagtgaccaa attt | 804 |
| | <210> 11 | |
| | <211> 708 | |
| | <212> DNA | |
| 35 | <213> Homo sapiens | |

12.

<400> 11

| | | | | | | | |
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| | gagccgtccg | cgcccggcgg | cgcggggagc | ccaggagcct | gccccgccct | ggggacgaag | 120 |
| 5 | agctgcagct | cctcctgtgc | ggtgcacgat | ctgattttct | ggagagatgt | gaagaagact | 180 |
| | gggtttgtct | ttggcaccac | gctgatcatg | ctgctttccc | tggcagcttt | cagtgtcatc | 240 |
| | agtgtggttt | cttacctcat | cctggctctt | ctctctgtca | ccatcagctt | caggatctac | 300 |
| | aagtccgtca | tccaagctgt | acagaagtca | gaagaaggcc | atccattcaa | agcctacctg | 360 |
| | gacgtagaca | ttactctgtc | ctcagaagct | ttccataatt | acatgaatgc | tgccatgggtg | 420 |
| 10 | cacatcaaca | gggcccgtgaa | actcattatt | cgtctctttc | tggtagaaga | tctggttgac | 480 |
| | tccttgaaagc | tggtgtctt | catgtggctg | atgacctatg | ttggtgctgt | ttttaacgga | 540 |
| | atcacccctc | taattcttgc | tgaactgctc | attttcagt | tcccattgt | ctatgagaag | 600 |
| | tacaagaccc | agattgatca | ctatgttggc | atcgcccgag | atcagaccaa | gtcaattgtt | 660 |
| | gaaaagatcc | aagcaaaact | ccttggaatc | gccaaaaaaa | aggcagaa | | 708 |

15

<210> 12

<211> 783

<212> DNA

<213> Homo sapiens

20

<400> 12

| | | | | | | | |
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| | gttatcatca | ctttcttcgt | aggcatgatc | cgccactacg | tgtccatcct | gctgcagagc | 120 |
| | gacaagaagc | tcaccagga | acaagtatct | gacagtcaag | tcctaattcg | aagcagagtc | 180 |
| 25 | ctcagggaaa | atggaaaata | cattcccaaa | cagtctttct | tgacacgaaa | atattatttc | 240 |
| | aacaaccag | aggatggatt | tttcaaaaaa | actaaacgga | aggtagtgcc | accttctcct | 300 |
| | atgactgatc | ctactatgtt | gacagacatg | atgaaaggga | atgtaacaaa | tgtcctcct | 360 |
| | atgattctta | ttggtggatg | gatcaacatg | acattctcag | gctttgtcac | aaccaaggtc | 420 |
| | ccatttcac | tgacctccg | ttttaagcct | atgttacagc | aaggaatcga | gctactcaca | 480 |
| 30 | ttagatgcat | cctgggtgag | ttctgcatcc | tggtaactcc | tcaatgtatt | tgggttcgg | 540 |
| | agcatttact | ctctgattct | gggccaagat | aatgccgtg | accaatcacg | aatgatgcag | 600 |
| | gagcagatga | cgggagcagc | catggccatg | ccgcagaca | caaacaaagc | tttcaagaca | 660 |
| | gagtgggaag | ctttggagct | gacggatcac | cagtgggcac | tagatgatgt | cgaagaagag | 720 |
| | ctcatggcca | aagacctoca | cttcgaaggc | atgttcaaaa | aggaattaca | gacctctatt | 780 |
| 35 | ttt | | | | | | 783 |

<210> 13
 <211> 984
 <212> DNA
 5 <213> Homo sapiens

<400> 13
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 10 agctttctac tcaacaggtc tatccaggaa aatggtgaac taaaaattga aagcaagatt 180
 gaagagatgg ttgaaccact aagagagaaa atcagagatt tagaaaaaag ctttaccag 240
 aaatacccac cagtaaagtt tttatcagaa aaggatcgga aaagaatttt gataacagga 300
 ggcgcagggt tcgtgggctc ccatctaact gacaaactca tgatggacgg ccacgagggtg 360
 accgtggtgg acaatttctt cacgggcagg aagagaaacg tggagcactg gatcggacat 420
 15 gagaacttcg agttgattaa ccacgacgtg gtggagcccc tctacatcga gggcgtggaa 480
 gtgcgagtgg ccagaatctt caacaccttt gggccacgca tgcacatgaa cgatgggcga 540
 gtagtcagca acttcatcct gcaggcgctc cagggggagc cactcacggt atacggatcc 600
 ggggtctcaga caagggcggt ccagtacgtc agcgatctag tgaatggcct cgtggctctc 660
 atgaacagca acgtcagcag cccggccaac ctgggggaacc cagaagaaca cacaatccta 720
 20 gaatttgctc agttaattaa aaaccttggt ggtagcggaa gtgaaattca gtttctctcc 780
 gaagcccagg atgaccaca gaaaagaaaa ccagacatca aaaaagcaaa gctgatgctg 840
 ggggtgggagc ccgtgggtccc gctggaggaa ggtttaaaca aagcaattca ctacttccgt 900
 aaagaactcg agtaccaggc aaataatcag tacatcccca aaccaagcc tgccagaata 960
 aagaaaggac ggactcgcca cagc 984

25
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 <211> 900
 <212> DNA
 <213> Homo sapiens

30
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 tccttcgtga agctttttat tcctaagagg agaaaatcag tcaccggcga aatcgtgctg 120
 attacaggag ctgggcatgg aattgggaga ctgactgcct atgaatttgc taaacttaaa 180
 35 agcaagctgg ttctctggga tataaataag catggactgg aggaaacagc tgccaaatgc 240

| | | |
|----|---|-----|
| | aagggactgg gtgccaaggt tcataccttt gtggtagact gcagcaaccg agaagatatt | 300 |
| | tacagctctg caaagaaggt gaaggcagaa attggagatg ttagtatttt agtaaataat | 360 |
| | gctggtgtag tctatacatc agatttggtt gctacacaag atcctcagat tgaaaagact | 420 |
| | tttgaagtta atgtacttgc acatttctgg actacaaagg catttcttcc tgcaatgacg | 480 |
| 5 | aagaataacc atggccatat tgtcactgtg gcttcggcag ctggacatgt ctcggtcccc | 540 |
| | ttcttactgg cttactgttc aagcaagttt gctgctgttg gatttcataa aactttgaca | 600 |
| | gatgaactgg ctgccttaca aataactgga gtcaaaaaca catgtctgtg tctaatttc | 660 |
| | gtaaacactg gcttcatcaa aaatccaagt acaagtttgg gaccactct ggaacctgag | 720 |
| | gaagtggtaa acaggctgat gcatgggatt ctgactgagc agaagatgat ttttattcca | 780 |
| 10 | tcttctatag cttttttaac aacattggaa aggatccttc ctgagcgttt cctggcagtt | 840 |
| | ttaaaacgaa aaatcagtgt taagtttgat gcagttattg gatataaaat gaaagcgcaa | 900 |
| | <210> 15 | |
| | <211> 546 | |
| 15 | <212> DNA | |
| | <213> Homo sapiens | |
| | <400> 15 | |
| | atgaaaggct ggggttggct ggccctgctt ctgggggccc tgctgggaac cgcctgggct | 60 |
| 20 | cggaggagcc aggatctcca ctgtggagca tgcagggtc tggtggatga actagaatgg | 120 |
| | gaaattgccc aggtggacct caagaagacc attcagatgg gatctttccg gatcaatcca | 180 |
| | gatggcagcc agtcagtggg ggaggtgcct tatgcccgct cagaggccca cctcacagag | 240 |
| | ctgctggagg agatatgtga ccggatgaag gagtatgggg aacagattga tccttcacc | 300 |
| | catcgcaaga actacgtacg tgtagtgggc cggaatggag aatccagtga actggacct | 360 |
| 25 | caaggcatcc gaatcgactc agatatttagc ggcacctca agtttgcgtg tgagagcatt | 420 |
| | gtggaggaat acgaggatga actcattgaa ttcttttccc gagaggctga caatgttaaa | 480 |
| | gacaaacttt gcagtaagcg aacagatcct tgtgaccatg ccctgcacat atcgcatgat | 540 |
| | gagcta | |
| 30 | <210> 16 | |
| | <211> 198 | |
| | <212> DNA | |
| | <213> Homo sapiens | |
| 35 | <400> 16 | |

15.

| | | |
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| | agcgagggag ggaggcagaa cttcgatgtg aggcctcagt ctggggcaaa tgggcttccc | 120 |
| | aaacactcct actggttgga cctctggctt ttcctccttt tcgatgtggt ggtgtttctc | 180 |
| | tttgtgtatt ttttgcca | 198 |
| 5 | <210> 17 | |
| | <211> 549 | |
| | <212> DNA | |
| | <213> Homo sapiens | |
| 10 | <400> 17 | |
| | atggcgctctc gagcaggccc gcgagcggcc ggcaccgacg gcagcgactt tcagcaccgg | 60 |
| | gagcgcgctcg ccatgcacta ccagatgagt gtgacctca agtatgaaat caagaagctg | 120 |
| | atctacgtac atctggtcac atggctgctg ctggttgcta agatgagcgt gggacacctg | 180 |
| 15 | aggctcttgt caccatgatca ggtggccatg ccctatcagt ggaataccc gtatttgctg | 240 |
| | agcattttgc cctctctctt gggccttctc tcttttccc gcaacaacat tagctacctg | 300 |
| | gtgctctcca tgatcagcat gggactcttt tccatcgctc cactcattta tggcagcatg | 360 |
| | gagatgttcc ctgctgcaca gcagctctac cgccatggca aggcctaccg tttcctcttt | 420 |
| | ggtttttctg ccgtttccat catgtacctg gtgttggtgt tggcagtgca agtgcatgcc | 480 |
| 20 | tggcagttgt actacagcaa gaagctccta gactcttggt tcaccagcac acaggagaag | 540 |
| | aagcataaa | 549 |
| | <210> 18 | |
| | <211> 972 | |
| 25 | <212> DNA | |
| | <213> Homo sapiens | |
| | <400> 18 | |
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| 30 | cctccagtgc ctgtggggct ggaggtgaag ttgggggccc tgggtctgct gctggtgctc | 120 |
| | accctcctct gcagcctggt gccatctgt gtgctgcgcc ggccaggagc taaccatgaa | 180 |
| | ggctcagctt ccgcocagaa agccttgagc ctagtaagct gtttcgcggg gggcgtcttt | 240 |
| | ttggccactt gtctcttgga cctgctgctt gactacctgg ctgccataga tgaggccctg | 300 |
| | gcagccttgc acgtgacgct ccagttccca ctgcaagagt tcctcctggc catgggcttc | 360 |
| 35 | ttcctggctc tggatgatga gcagatcaca ctggcttaca aggagcagtc agggccgtca | 420 |

16.

| | | |
|----|--|-----|
| | cctctggagg aaacaagggc tctgctggga acagtgaatg gtgggcccga gcattggcat | 480 |
| | gatgggccag gggccccaca ggcgagtga gcccagcaa cccctcagc cttgcgtgcc | 540 |
| | tgtgtactgg tgttctccct ggccctccac tccgtgttcg aggggctggc ggtagggctg | 600 |
| | cagcgagacc gggctcgggc catggagctg tgccctggctt tgetgctcca caagggcatc | 660 |
| 5 | ctggctgtca gcctgtccct gcggtgttg cagagccacc ttagggcaca ggtggtggct | 720 |
| | ggctgtggga tcctcttctc atgcatgaca cctctaggca tcgggctggg tgcagctctg | 780 |
| | gcagagtcgg caggacctct gcaccagctg gccagctctg tgctagaggg catggcagct | 840 |
| | ggcaccttct tctatatcac ctttctggaa atcctgcccc aggagctggc cagttctgag | 900 |
| | caaaggatcc tcaaggtcat tctgctccta gcaggctttg ccctgctcac tggcctgctc | 960 |
| 10 | ttcatccaaa tc | 972 |
| | <210> 19 | |
| | <211> 1705 | |
| | <212> DNA | |
| 15 | <213> Homo sapiens | |
| | <400> 19 | |
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| | atgagaaatt gatgcgagga tcaatacaag cttaatttga attaataaaa ggaaatattt | 120 |
| 20 | tctccctttg aacttatctc cgtaaagcca ttgtgcctcc tcttgggggt cacgtgttca | 180 |
| | caatca atg gcc ttt gag gag ctc ttg agt caa gtt gga ggc ctt ggg | 228 |
| | Met Ala Phe Glu Glu Leu Leu Ser Gln Val Gly Gly Leu Gly | |
| | 1 5 10 | |
| | aga ttt cag atg ctt cat ctg gtt ttt att ctt ccc tct ctc atg tta | 276 |
| 25 | Arg Phe Gln Met Leu His Leu Val Phe Ile Leu Pro Ser Leu Met Leu | |
| | 15 20 25 30 | |
| | tta atc cct cat ata ctg cta gag aac ttt gct gca gcc att cct ggt | 324 |
| | Leu Ile Pro His Ile Leu Leu Glu Asn Phe Ala Ala Ala Ile Pro Gly | |
| | 35 40 45 | |
| 30 | cat cgt tgc tgg gtc cac atg ctg gac aat aat act gga tct ggt aat | 372 |
| | His Arg Cys Trp Val His Met Leu Asp Asn Asn Thr Gly Ser Gly Asn | |
| | 50 55 60 | |
| | gaa act gga atc ctc agt gaa gat gcc ctc ttg aga atc tct atc cca | 420 |
| | Glu Thr Gly Ile Leu Ser Glu Asp Ala Leu Leu Arg Ile Ser Ile Pro | |
| 35 | 65 70 75 | |

17.

| | | |
|----|--|------|
| | cta gac tca aat ctg agg cca gag aag tgt cgt cgc ttt gtc cat ccc | 468 |
| | Leu Asp Ser Asn Leu Arg Pro Glu Lys Cys Arg Arg Phe Val His Pro | |
| | 80 85 90 | |
| | cag tgg cag ctt ctt cac ctg aat ggg act atc cac agc aca agt gag | 516 |
| 5 | Gln Trp Gln Leu Leu His Leu Asn Gly Thr Ile His Ser Thr Ser Glu | |
| | 95 100 105 110 | |
| | gca gac aca gaa ccc tgt gtg gat ggc tgg gta tat gat caa agc tac | 564 |
| | Ala Asp Thr Glu Pro Cys Val Asp Gly Trp Val Tyr Asp Gln Ser Tyr | |
| | 115 120 125 | |
| 10 | ttc cct tcg acc att gtg act aag tgg gac ctg gta tgt gat tat cag | 612 |
| | Phe Pro Ser Thr Ile Val Thr Lys Trp Asp Leu Val Cys Asp Tyr Gln | |
| | 130 135 140 | |
| | tca ctg aaa tca gtg gtt caa ttc cta ctt ctg act gga atg ctg gtg | 660 |
| | Ser Leu Lys Ser Val Val Gln Phe Leu Leu Leu Thr Gly Met Leu Val | |
| 15 | 145 150 155 | |
| | gga ggc atc ata ggt ggc cat gtc tca gac agg tgg ctg gtg gaa tct | 708 |
| | Gly Gly Ile Ile Gly Gly His Val Ser Asp Arg Trp Leu Val Glu Ser | |
| | 160 165 170 | |
| | gct cgg tgg ttg ata atc acc aat aaa cta gat gag ggc tta aag gca | 756 |
| 20 | Ala Arg Trp Leu Ile Ile Thr Asn Lys Leu Asp Glu Gly Leu Lys Ala | |
| | 175 180 185 190 | |
| | ctt aga aaa gtt gca cgc aca aat gga ata aag aat gct gaa gaa acc | 804 |
| | Leu Arg Lys Val Ala Arg Thr Asn Gly Ile Lys Asn Ala Glu Glu Thr | |
| | 195 200 205 | |
| 25 | ctg aac ata gag gtt gta aga tcc acc atg cag gag gag ctg gat gca | 852 |
| | Leu Asn Ile Glu Val Val Arg Ser Thr Met Gln Glu Glu Leu Asp Ala | |
| | 210 215 220 | |
| | gca cag acc aaa act act gtg tgt gac ttg ttc cgc aac ccc agt atg | 900 |
| | Ala Gln Thr Lys Thr Thr Val Cys Asp Leu Phe Arg Asn Pro Ser Met | |
| 30 | 225 230 235 | |
| | cgt aaa agg atc tgt atc ctg gta ttt ttg aga aaa aaa atc tca agg | 948 |
| | Arg Lys Arg Ile Cys Ile Leu Val Phe Leu Arg Lys Lys Ile Ser Arg | |
| | 240 245 250 | |
| | aaa agg cat aaa aat gat tgc tac aca aaa gtg acc aaa ttt taagaagcct | 1000 |
| 35 | Lys Arg His Lys Asn Asp Cys Tyr Thr Lys Val Thr Lys Phe | |

| | | | | |
|----|---|-------------|------------|---------------------------------------|
| | 255 | 260 | 265 | |
| | tcatgagctg | attggtgggg | aaattcagaa | aaaaaaatac aggaaaagaa cacaccagaa 1060 |
| | gggttttttt | ccctacaacc | agcaagaaca | tatattagat acatgaatct caattataat 1120 |
| | tatggcatta | atttgcattt | tatttcaaaa | ttaacttgtg gggacatgta atctcttgag 1180 |
| 5 | caatctgata | tttttgggaa | gtccttttaa | aagttacaaa tttatcaata aattactagt 1240 |
| | agataagatg | attcagaaac | aaaagaaaat | cacagaatta ggatgtggct ggctggtgta 1300 |
| | tgaagcacca | tgtgatgaat | tcataaaagt | gcaaaagtca aaacaatact gtacatgcaa 1360 |
| | ccagaaatca | aaataaatcc | agaaatagag | acctatataa atgcatttaa tacatgatac 1420 |
| | ttttgacata | ataagccatt | ggaaaacgga | aagattagat actaaataac attgactatc 1480 |
| 10 | tctttgtaaa | tacagtcact | aaatgatgtt | agttactttt ccatggtgga attttaatta 1540 |
| | ctttttcttt | gtaatttttc | tctctgtata | ttttaacaa atagctggta tagtttacia 1600 |
| | tattataaag | atattgttca | aattgaaggg | caaaggccag gttcagcaat tttcaaactg 1660 |
| | tatgtacatt | taataaaaata | actataaatt | aaaaaattat atttc 1705 |
| 15 | <210> 20 | | | |
| | <211> 268 | | | |
| | <212> PRT | | | |
| | <213> Homo sapiens | | | |
| 20 | <400> 20 | | | |
| | Met Ala Phe Glu Glu Leu Leu Ser Gln Val Gly Gly Leu Gly | | | |
| | 1 | 5 | 10 | |
| | Arg Phe Gln Met Leu His Leu Val Phe Ile Leu Pro Ser Leu Met Leu | | | |
| | 15 | 20 | 25 | 30 |
| 25 | Leu Ile Pro His Ile Leu Leu Glu Asn Phe Ala Ala Ala Ile Pro Gly | | | |
| | 35 | 40 | 45 | |
| | His Arg Cys Trp Val His Met Leu Asp Asn Asn Thr Gly Ser Gly Asn | | | |
| | 50 | 55 | 60 | |
| | Glu Thr Gly Ile Leu Ser Glu Asp Ala Leu Leu Arg Ile Ser Ile Pro | | | |
| 30 | 65 | 70 | 75 | |
| | Leu Asp Ser Asn Leu Arg Pro Glu Lys Cys Arg Arg Phe Val His Pro | | | |
| | 80 | 85 | 90 | |
| | Gln Trp Gln Leu Leu His Leu Asn Gly Thr Ile His Ser Thr Ser Glu | | | |
| | 95 | 100 | 105 | 110 |
| 35 | Ala Asp Thr Glu Pro Cys Val Asp Gly Trp Val Tyr Asp Gln Ser Tyr | | | |

19.

| | | | | | | | | | | | | | | | | | |
|----|--------------------|------------|------------|------------|------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | | | 115 | | | | | 120 | | | | | | 125 | |
| | Phe | Pro | Ser | Thr | Ile | Val | Thr | Lys | Trp | Asp | Leu | Val | Cys | Asp | Tyr | Gln | |
| | | | | | 130 | | | | | 135 | | | | | | 140 | |
| | Ser | Leu | Lys | Ser | Val | Val | Gln | Phe | Leu | Leu | Leu | Thr | Gly | Met | Leu | Val | |
| 5 | | | 145 | | | | | | 150 | | | | | 155 | | | |
| | Gly | Gly | Ile | Ile | Gly | Gly | His | Val | Ser | Asp | Arg | Trp | Leu | Val | Glu | Ser | |
| | | 160 | | | | | 165 | | | | | | 170 | | | | |
| | Ala | Arg | Trp | Leu | Ile | Ile | Thr | Asn | Lys | Leu | Asp | Glu | Gly | Leu | Lys | Ala | |
| | 175 | | | | | 180 | | | | | 185 | | | | | 190 | |
| 10 | Leu | Arg | Lys | Val | Ala | Arg | Thr | Asn | Gly | Ile | Lys | Asn | Ala | Glu | Glu | Thr | |
| | | | | 195 | | | | | | 200 | | | | | 205 | | |
| | Leu | Asn | Ile | Glu | Val | Val | Arg | Ser | Thr | Met | Gln | Glu | Glu | Leu | Asp | Ala | |
| | | | 210 | | | | | 215 | | | | | 220 | | | | |
| | Ala | Gln | Thr | Lys | Thr | Thr | Val | Cys | Asp | Leu | Phe | Arg | Asn | Pro | Ser | Met | |
| 15 | | 225 | | | | | 230 | | | | | 235 | | | | | |
| | Arg | Lys | Arg | Ile | Cys | Ile | Leu | Val | Phe | Leu | Arg | Lys | Lys | Ile | Ser | Arg | |
| | | 240 | | | | | 245 | | | | | 250 | | | | | |
| | Lys | Arg | His | Lys | Asn | Asp | Cys | Tyr | Thr | Lys | Val | Thr | Lys | Phe | | | |
| | 255 | | | | 260 | | | | | 265 | | | | | | | |
| 20 | | | | | | | | | | | | | | | | | |
| | <210> 21 | | | | | | | | | | | | | | | | |
| | <211> 1759 | | | | | | | | | | | | | | | | |
| | <212> DNA | | | | | | | | | | | | | | | | |
| | <213> Homo sapiens | | | | | | | | | | | | | | | | |
| 25 | | | | | | | | | | | | | | | | | |
| | <400> 21 | | | | | | | | | | | | | | | | |
| | agtcagtctg | tcggagtctg | tcctcggagc | aggcggagta | aagggacttg | agcgagccag | | | | | | | | | | | 60 |
| | ttgccggatt | attctatttc | ccctccctct | ctccgcgcc | gtatctcttt | tcaccttct | | | | | | | | | | | 120 |
| | cccacccctg | ctcgcgtagc | c atg | gcg gag | ccg tcg | gcg gcc | act | cag | tcc | | | | | | | | 171 |
| 30 | | | | Met | Ala | Glu | Pro | Ser | Ala | Ala | Thr | Gln | Ser | | | | |
| | | | | 1 | | | 5 | | | | | 10 | | | | | |
| | cat | tcc | atc | tcc | tcg | tcg | tcc | ttc | gga | gcc | gag | ccg | tcc | gcg | ccc | ggc | 219 |
| | His | Ser | Ile | Ser | Ser | Ser | Ser | Phe | Gly | Ala | Glu | Pro | Ser | Ala | Pro | Gly | |
| | | | | 15 | | | 20 | | | | | 25 | | | | | |
| 35 | ggc | ggc | ggg | agc | cca | gga | gcc | tgc | ccc | gcc | ctg | ggg | acg | aag | agc | tgc | 267 |

20

| | | |
|----|---|-----|
| | Gly Gly Gly Ser Pro Gly Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys | |
| | 30 35 40 | |
| | agc tcc tcc tgt gcg gtg cac gat ctg att ttc tgg aga gat gtg aag | 315 |
| | Ser Ser Ser Cys Ala Val His Asp Leu Ile Phe Trp Arg Asp Val Lys | |
| 5 | 45 50 55 | |
| | aag act ggg ttt gtc ttt ggc acc acg ctg atc atg ctg ctt tcc ctg | 363 |
| | Lys Thr Gly Phe Val Phe Gly Thr Thr Leu Ile Met Leu Leu Ser Leu | |
| | 60 65 70 | |
| | gca gct ttc agt gtc atc agt gtg gtt tct tac ctc atc ctg gct ctt | 411 |
| 10 | Ala Ala Phe Ser Val Ile Ser Val Val Ser Tyr Leu Ile Leu Ala Leu | |
| | 75 80 85 90 | |
| | ctc tct gtc acc atc agc ttc agg atc tac aag tcc gtc atc caa gct | 459 |
| | Leu Ser Val Thr Ile Ser Phe Arg Ile Tyr Lys Ser Val Ile Gln Ala | |
| | 95 100 105 | |
| 15 | gta cag aag tca gaa gaa ggc cat cca ttc aaa gcc tac ctg gac gta | 507 |
| | Val Gln Lys Ser Glu Glu Gly His Pro Phe Lys Ala Tyr Leu Asp Val | |
| | 110 115 120 | |
| | gac att act ctg tcc tca gaa gct ttc cat aat tac atg aat gct gcc | 555 |
| | Asp Ile Thr Leu Ser Ser Glu Ala Phe His Asn Tyr Met Asn Ala Ala | |
| 20 | 125 130 135 | |
| | atg gtg cac atc aac agg gcc ctg aaa ctc att att cgt ctc ttt ctg | 603 |
| | Met Val His Ile Asn Arg Ala Leu Lys Leu Ile Ile Arg Leu Phe Leu | |
| | 140 145 150 | |
| | gta gaa gat ctg gtt gac tcc ttg aag ctg gct gtc ttc atg tgg ctg | 651 |
| 25 | Val Glu Asp Leu Val Asp Ser Leu Lys Leu Ala Val Phe Met Trp Leu | |
| | 155 160 165 170 | |
| | atg acc tat gtt ggt gct gtt ttt aac gga atc acc ctt cta att ctt | 699 |
| | Met Thr Tyr Val Gly Ala Val Phe Asn Gly Ile Thr Leu Leu Ile Leu | |
| | 175 180 185 | |
| 30 | gct gaa ctg ctc att ttc agt gtc ccg att gtc tat gag aag tac aag | 747 |
| | Ala Glu Leu Leu Ile Phe Ser Val Pro Ile Val Tyr Glu Lys Tyr Lys | |
| | 190 195 200 | |
| | acc cag att gat cac tat gtt ggc atc gcc cga gat cag acc aag tca | 795 |
| | Thr Gln Ile Asp His Tyr Val Gly Ile Ala Arg Asp Gln Thr Lys Ser | |
| 35 | 205 210 215 | |

| | | |
|----|--|------|
| | att gtt gaa aag atc caa gca aaa ctc cct gga atc gcc aaa aaa aag | 843 |
| | Ile Val Glu Lys Ile Gln Ala Lys Leu Pro Gly Ile Ala Lys Lys Lys | |
| | 220 225 230 | |
| 5 | gca gaa taagtacatg gaaaccagaa atgcaacagt tactaaaaca ccatttaata g | 900 |
| | Ala Glu | |
| | 235 | |
| | ttataacgtc gttacttgta ctatgaagga aaatactoag tgtcagcttg agcctgcatt | 960 |
| | ccaagctttt tttttaattt ggtgttttct cccatccttt ccccttaacc ctcagtatca | 1020 |
| | agcacaaaaa ttgatggact gataaaagaa ctatcttaga actcagaaga agaaagaatc | 1080 |
| 10 | aaattcatag gataagtcaa taccttaatg gtggtagagc ctttacctgt agcttgaaag | 1140 |
| | gggaaagatt ggaggaaga gagaaaatga aagaacacct ctgggtcctt ctgtccagtt | 1200 |
| | ttcagcacta gtcttactca gctatccatt atagttttgc ccttaagaag tcatgattaa | 1260 |
| | cttatgaaaa aattatttgg ggacaggagt gtgatacctt ccttggtttt tttttgcagc | 1320 |
| | cctcaaatcc tatcttctctg cccacaaatg tgagcagcta cccctgatac tccttttctt | 1380 |
| 15 | taatgattta actatcaact tgataaataa cttataggtg atagtataa ttcctgattc | 1440 |
| | caagaatgcc atctgataaa aaagaataga aatggaaagt gggactgaga gggagtcagc | 1500 |
| | aggcatgctg cgggtggcgg cactccctct gactatcc ccagggaagg aaaggctccg | 1560 |
| | ccatttgga aagtggtttc tacgtcactg gacaccggtt ctgagcatta gtttgagaac | 1620 |
| | tcgttccoga atgtgctttc ctccctctcc cctgcccacc tcaagtttaa taaataaggt | 1680 |
| 20 | tgtacttttc ttactataaa ataaatgtct gtaactgctg tgcaactgctg taaacttggt | 1740 |
| | agagaaaaaa ataacctgc | 1759 |
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| | <211> 236 | |
| 25 | <212> PRT | |
| | <213> Homo sapiens | |
| | <400> 22 | |
| | Met Ala Glu Pro Ser Ala Ala Thr Gln Ser | |
| 30 | 1 5 10 | |
| | His Ser Ile Ser Ser Ser Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly | |
| | 15 20 25 | |
| | Gly Gly Gly Ser Pro Gly Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys | |
| | 30 35 40 | |
| 35 | Ser Ser Ser Cys Ala Val His Asp Leu Ile Phe Trp Arg Asp Val Lys | |

| | | | | |
|----|---|-----|-----|-----|
| | 45 | 50 | 55 | |
| | Lys Thr Gly Phe Val Phe Gly Thr Thr Leu Ile Met Leu Leu Ser Leu | | | |
| | 60 | 65 | 70 | |
| | Ala Ala Phe Ser Val Ile Ser Val Val Ser Tyr Leu Ile Leu Ala Leu | | | |
| 5 | 75 | 80 | 85 | 90 |
| | Leu Ser Val Thr Ile Ser Phe Arg Ile Tyr Lys Ser Val Ile Gln Ala | | | |
| | 95 | 100 | 105 | |
| | Val Gln Lys Ser Glu Glu Gly His Pro Phe Lys Ala Tyr Leu Asp Val | | | |
| | 110 | 115 | 120 | |
| 10 | Asp Ile Thr Leu Ser Ser Glu Ala Phe His Asn Tyr Met Asn Ala Ala | | | |
| | 125 | 130 | 135 | |
| | Met Val His Ile Asn Arg Ala Leu Lys Leu Ile Ile Arg Leu Phe Leu | | | |
| | 140 | 145 | 150 | |
| | Val Glu Asp Leu Val Asp Ser Leu Lys Leu Ala Val Phe Met Trp Leu | | | |
| 15 | 155 | 160 | 165 | 170 |
| | Met Thr Tyr Val Gly Ala Val Phe Asn Gly Ile Thr Leu Leu Ile Leu | | | |
| | 175 | 180 | 185 | |
| | Ala Glu Leu Leu Ile Phe Ser Val Pro Ile Val Tyr Glu Lys Tyr Lys | | | |
| | 190 | 195 | 200 | |
| 20 | Thr Gln Ile Asp His Tyr Val Gly Ile Ala Arg Asp Gln Thr Lys Ser | | | |
| | 205 | 210 | 215 | |
| | Ile Val Glu Lys Ile Gln Ala Lys Leu Pro Gly Ile Ala Lys Lys Lys | | | |
| | 220 | 225 | 230 | |
| | Ala Glu | | | |
| 25 | 235 | | | |
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| | <212> DNA | | | |
| 30 | <213> Homo sapiens | | | |
| | <400> 23 | | | |
| | agtggaagac caggcagccc agctgaaggc agtaagctcg gctcacagtc gcaggagagt | 60 | | |
| | tctgggggtac acgggcaaag gggcttgaga aggcccgag gcgaagccga agagaagcaa | 120 | | |
| 35 | ctgtgccccg gagaagagaa gctcgcccat tccagactgg gaaccagctt tcagtgaag | 179 | | |

| | | |
|----|---|-----|
| | atg gca ggg cca gaa ctg ttg ctc gac tcc aac atc cgc ctc tgg gtg | 227 |
| | Met Ala Gly Pro Glu Leu Leu Leu Asp Ser Asn Ile Arg Leu Trp Val | |
| | 1 5 10 15 | |
| | gtc cta ccc atc gtt atc atc act ttc ttc gta ggc atg atc cgc cac | 275 |
| 5 | Val Leu Pro Ile Val Ile Ile Thr Phe Phe Val Gly Met Ile Arg His | |
| | 20 25 30 | |
| | tac gtg tcc atc ctg ctg cag agc gac aag aag ctc acc cag gaa caa | 323 |
| | Tyr Val Ser Ile Leu Leu Gln Ser Asp Lys Lys Leu Thr Gln Glu Gln | |
| | 35 40 45 | |
| 10 | gta tct gac agt caa gtc cta att cga agc aga gtc ctc agg gaa aat | 371 |
| | Val Ser Asp Ser Gln Val Leu Ile Arg Ser Arg Val Leu Arg Glu Asn | |
| | 50 55 60 | |
| | gga aaa tac att ccc aaa cag tct ttc ttg aca cga aaa tat tat ttc | 419 |
| | Gly Lys Tyr Ile Pro Lys Gln Ser Phe Leu Thr Arg Lys Tyr Tyr Phe | |
| 15 | 65 70 75 80 | |
| | aac aac cca gag gat gga ttt ttc aaa aaa act aaa cgg aag gta gtg | 467 |
| | Asn Asn Pro Glu Asp Gly Phe Phe Lys Lys Thr Lys Arg Lys Val Val | |
| | 85 90 95 | |
| | cca cct tct cct atg act gat cct act atg ttg aca gac atg atg aaa | 515 |
| 20 | Pro Pro Ser Pro Met Thr Asp Pro Thr Met Leu Thr Asp Met Met Lys | |
| | 100 105 110 | |
| | ggg aat gta aca aat gtc ctc cct atg att ctt att ggt gga tgg atc | 563 |
| | Gly Asn Val Thr Asn Val Leu Pro Met Ile Leu Ile Gly Gly Trp Ile | |
| | 115 120 125 | |
| 25 | aac atg aca ttc tca ggc ttt gtc aca acc aag gtc cca ttt cca ctg | 611 |
| | Asn Met Thr Phe Ser Gly Phe Val Thr Thr Lys Val Pro Phe Pro Leu | |
| | 130 135 140 | |
| | acc ctc cgt ttt aag cct atg tta cag caa gga atc gag cta ctc aca | 659 |
| | Thr Leu Arg Phe Lys Pro Met Leu Gln Gln Gly Ile Glu Leu Leu Thr | |
| 30 | 145 150 155 160 | |
| | tta gat gca tcc tgg gtg agt tct gca tcc tgg tac ttc ctc aat gta | 707 |
| | Leu Asp Ala Ser Trp Val Ser Ser Ala Ser Trp Tyr Phe Leu Asn Val | |
| | 165 170 175 | |
| | ttt ggg ctt cgg agc att tac tct ctg att ctg ggc caa gat aat gcc | 755 |
| 35 | Phe Gly Leu Arg Ser Ile Tyr Ser Leu Ile Leu Gly Gln Asp Asn Ala | |

| | | | | |
|----|---|------|-----|-----|
| | 180 | 185 | 190 | |
| | gct gac caa tca cga atg atg cag gag cag atg acg gga gca gcc atg | 803 | | |
| | Ala Asp Gln Ser Arg Met Met Gln Glu Gln Met Thr Gly Ala Ala Met. | | | |
| | 195 | 200 | 205 | |
| 5 | gcc atg ccc gca gac aca aac aaa gct ttc aag aca gag tgg gaa gct | 851 | | |
| | Ala Met Pro Ala Asp Thr Asn Lys Ala Phe Lys Thr Glu Trp Glu Ala | | | |
| | 210 | 215 | 220 | |
| | ttg gag ctg acg gat cac cag tgg gca cta gat gat gtc gaa gaa gag | 899 | | |
| | Leu Glu Leu Thr Asp His Gln Trp Ala Leu Asp Asp Val Glu Glu Glu | | | |
| 10 | 225 | 230 | 235 | 240 |
| | ctc atg gcc aaa gac ctc cac ttc gaa ggc atg ttc aaa aag gaa tta | 947 | | |
| | Leu Met Ala Lys Asp Leu His Phe Glu Gly Met Phe Lys Lys Glu Leu | | | |
| | 245 | 250 | 255 | |
| | cag acc tct att ttt tgaagaccga gcagggatta gctgtgtcag gaacttgg | 1000 | | |
| 15 | Gln Thr Ser Ile Phe | | | |
| | 260 | | | |
| | agttgcactt aaccttgtaa ctttggttgg agctggcacc tcttgaaaca aaaaggagga | 1060 | | |
| | tgcacgagc | 1069 | | |
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| | <212> PRT | | | |
| | <213> Homo sapiens | | | |
| 25 | <400> 24 | | | |
| | Met Ala Gly Pro Glu Leu Leu Leu Asp Ser Asn Ile Arg Leu Trp Val | | | |
| | 1 5 10 15 | | | |
| | Val Leu Pro Ile Val Ile Ile Thr Phe Phe Val Gly Met Ile Arg His | | | |
| | 20 25 30 | | | |
| 30 | Tyr Val Ser Ile Leu Leu Gln Ser Asp Lys Lys Leu Thr Gln Glu Gln | | | |
| | 35 40 45 | | | |
| | Val Ser Asp Ser Gln Val Leu Ile Arg Ser Arg Val Leu Arg Glu Asn | | | |
| | 50 55 60 | | | |
| | Gly Lys Tyr Ile Pro Lys Gln Ser Phe Leu Thr Arg Lys Tyr Tyr Phe | | | |
| 35 | 65 70 75 80 | | | |

[illegible]

| | | |
|----|---|-----|
| | agg atg aag ctg ctg ggc atc gcc ttg ctg gcc tac gtc gcc tct | 154 |
| | Arg Met Lys Leu Leu Leu Gly Ile Ala Leu Leu Ala Tyr Val Ala Ser | |
| | 20 25 30 | |
| | gtt tgg ggc aac ttc gtt aat atg agc ttt cta ctc aac agg tct atc | 202 |
| 5 | Val Trp Gly Asn Phe Val Asn Met Ser Phe Leu Leu Asn Arg Ser Ile | |
| | 35 40 45 | |
| | cag gaa aat ggt gaa cta aaa att gaa agc aag att gaa gag atg gtt | 250 |
| | Gln Glu Asn Gly Glu Leu Lys Ile Glu Ser Lys Ile Glu Glu Met Val | |
| | 50 55 60 | |
| 10 | gaa cca cta aga gag aaa atc aga gat tta gaa aaa agc ttt acc cag | 298 |
| | Glu Pro Leu Arg Glu Lys Ile Arg Asp Leu Glu Lys Ser Phe Thr Gln | |
| | 65 70 75 80 | |
| | aaa tac cca cca gta aag ttt tta tca gaa aag gat cgg aaa aga att | 346 |
| | Lys Tyr Pro Pro Val Lys Phe Leu Ser Glu Lys Asp Arg Lys Arg Ile | |
| 15 | 85 90 95 | |
| | ttg ata aca gga ggc gca ggg ttc gtg ggc tcc cat cta act gac aaa | 394 |
| | Leu Ile Thr Gly Gly Ala Gly Phe Val Gly Ser His Leu Thr Asp Lys | |
| | 100 105 110 | |
| | ctc atg atg gac ggc cac gag gtg acc gtg gtg gac aat ttc ttc acg | 442 |
| 20 | Leu Met Met Asp Gly His Glu Val Thr Val Val Asp Asn Phe Phe Thr | |
| | 115 120 125 | |
| | ggc agg aag aga aac gtg gag cac tgg atc gga cat gag aac ttc gag | 490 |
| | Gly Arg Lys Arg Asn Val Glu His Trp Ile Gly His Glu Asn Phe Glu | |
| | 130 135 140 | |
| 25 | ttg att aac cac gac gtg gtg gag ccc ctc tac atc gag ggc gtg gaa | 538 |
| | Leu Ile Asn His Asp Val Val Glu Pro Leu Tyr Ile Glu Gly Val Glu | |
| | 145 150 155 160 | |
| | gtg cga gtg gcc aga atc ttc aac acc ttt ggg cca cgc atg cac atg | 586 |
| | Val Arg Val Ala Arg Ile Phe Asn Thr Phe Gly Pro Arg Met His Met | |
| 30 | 165 170 175 | |
| | aac gat ggg cga gta gtc agc aac ttc atc ctg cag gcg ctc cag ggg | 634 |
| | Asn Asp Gly Arg Val Val Ser Asn Phe Ile Leu Gln Ala Leu Gln Gly | |
| | 180 185 190 | |
| | gag cca ctc acg gta tac gga tcc ggg tct cag aca agg gcg ttc cag | 682 |
| 35 | Glu Pro Leu Thr Val Tyr Gly Ser Gly Ser Gln Thr Arg Ala Phe Gln | |

| | | | | |
|----|--|------|-----|-----|
| | 195 | 200 | 205 | |
| | tac gtc agc gat cta gtg aat ggc ctc gtg gct ctc atg aac agc aac | 730 | | |
| | Tyr Val Ser Asp Leu Val Asn Gly Leu Val Ala Leu Met Asn Ser Asn | | | |
| | 210 | 215 | 220 | |
| 5 | gtc agc agc ccg gtc aac ctg ggg aac cca gaa gaa cac aca atc cta | 778 | | |
| | Val Ser Ser Pro Val Asn Leu Gly Asn Pro Glu Glu His Thr Ile Leu | | | |
| | 225 | 230 | 235 | 240 |
| | gaa ttt gct cag tta att aaa aac ctt gtt ggt agc gga agt gaa att | 826 | | |
| | Glu Phe Ala Gln Leu Ile Lys Asn Leu Val Gly Ser Gly Ser Glu Ile | | | |
| 10 | 245 | 250 | 255 | |
| | cag ttt ctc tcc gaa gcc cag gat gac cca cag aaa aga aaa cca gac | 874 | | |
| | Gln Phe Leu Ser Glu Ala Gln Asp Asp Pro Gln Lys Arg Lys Pro Asp | | | |
| | 260 | 265 | 270 | |
| | atc aaa aaa gca aag ctg atg ctg ggg tgg gag ccc gtg gtc ccg ctg | 922 | | |
| 15 | Ile Lys Lys Ala Lys Leu Met Leu Gly Trp Glu Pro Val Val Pro Leu | | | |
| | 275 | 280 | 285 | |
| | gag gaa ggt tta aac aaa gca att cac tac ttc cgt aaa gaa ctc gag | 970 | | |
| | Glu Glu Gly Leu Asn Lys Ala Ile His Tyr Phe Arg Lys Glu Leu Glu | | | |
| | 290 | 295 | 300 | |
| 20 | tac cag gca aat aat cag tac atc ccc aaa cca aag cct gcc aga ata | 1018 | | |
| | Tyr Gln Ala Asn Asn Gln Tyr Ile Pro Lys Pro Lys Pro Ala Arg Ile | | | |
| | 305 | 310 | 315 | 320 |
| | aag aaa gga cgg act cgc cac agc tgaactctc acttttagga cacaagac | 1070 | | |
| | Lys Lys Gly Arg Thr Arg His Ser | | | |
| 25 | 325 | | | |
| | taccattgta cacttgatgg gatgtatttt tggctttttt ttgttgtcgt ttaaagaaag | 1130 | | |
| | actttaacag gtgtcatgaa gaacaaaactg gaatttcatt ctgaagcttg ctttaatgaa | 1190 | | |
| | atggatgtgc ctaaaagctc ccctcaaaaa actgcagatt ttgccttgca ctttttgaat | 1250 | | |
| | ctctcttttt atgtaaaata gcgtagatgc atctctgcgt attttcaagt ttttttatct | 1310 | | |
| 30 | tgctgtgaga gcatatgttg tgactgtcgt tgacagtttt atttactggt ttctttgtga | 1370 | | |
| | agctgaaaag gaacattaag cgggacaaaa aatgccgatt ttatttataa aagtgggtac | 1430 | | |
| | ttaataaatg agtcgttata ctatgcataa agaaaaatcc tagcagtatt gtcaggtggt | 1490 | | |
| | ggtgcgccgg cattgatttt agggcagata aaagaattct gtgtgagagc tttatgtttc | 1550 | | |
| | tcttttaatt cagagttttt ccaaggtcta cttttgagtt gcaaacttga ctttgaaata | 1610 | | |
| 35 | ttcctgttgg tcatgatcaa ggatatttga aatcactact gtgttttgct gcgtatctgg | 1670 | | |

ggcgggggca ggttgggggg cacaaggtta acatattctt ggttaaccat ggttaaatat 1730
gctatttttaa taaaatattg aaactcacc 1759

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<212> PRT

<213> Homo sapiens

<400> 26

10 Met Val Ser Lys Ala Leu Leu Arg Leu Val Ser Ala Val Asn Arg Arg
1 5 10 15
Arg Met Lys Leu Leu Leu Gly Ile Ala Leu Leu Ala Tyr Val Ala Ser
20 25 30
Val Trp Gly Asn Phe Val Asn Met Ser Phe Leu Leu Asn Arg Ser Ile
15 35 40 45
Gln Glu Asn Gly Glu Leu Lys Ile Glu Ser Lys Ile Glu Glu Met Val
50 55 60
Glu Pro Leu Arg Glu Lys Ile Arg Asp Leu Glu Lys Ser Phe Thr Gln
65 70 75 80
20 Lys Tyr Pro Pro Val Lys Phe Leu Ser Glu Lys Asp Arg Lys Arg Ile
85 90 95
Leu Ile Thr Gly Gly Ala Gly Phe Val Gly Ser His Leu Thr Asp Lys
100 105 110
Leu Met Met Asp Gly His Glu Val Thr Val Val Asp Asn Phe Phe Thr
25 115 120 125
Gly Arg Lys Arg Asn Val Glu His Trp Ile Gly His Glu Asn Phe Glu
130 135 140
Leu Ile Asn His Asp Val Val Glu Pro Leu Tyr Ile Glu Gly Val Glu
145 150 155 160
30 Val Arg Val Ala Arg Ile Phe Asn Thr Phe Gly Pro Arg Met His Met
165 170 175
Asn Asp Gly Arg Val Val Ser Asn Phe Ile Leu Gln Ala Leu Gln Gly
180 185 190
Glu Pro Leu Thr Val Tyr Gly Ser Gly Ser Gln Thr Arg Ala Phe Gln
35 195 200 205

| | | |
|----|---|-----|
| | Tyr Val Ser Asp Leu Val Asn Gly Leu Val Ala Leu Met Asn Ser Asn | |
| | 210 215 220 | |
| | Val Ser Ser Pro Val Asn Leu Gly Asn Pro Glu Glu His Thr Ile Leu | |
| | 225 230 235 240 | |
| 5 | Glu Phe Ala Gln Leu Ile Lys Asn Leu Val Gly Ser Gly Ser Glu Ile | |
| | 245 250 255 | |
| | Gln Phe Leu Ser Glu Ala Gln Asp Asp Pro Gln Lys Arg Lys Pro Asp | |
| | 260 265 270 | |
| | Ile Lys Lys Ala Lys Leu Met Leu Gly Trp Glu Pro Val Val Pro Leu | |
| 10 | 275 280 285 | |
| | Glu Glu Gly Leu Asn Lys Ala Ile His Tyr Phe Arg Lys Glu Leu Glu | |
| | 290 295 300 | |
| | Tyr Gln Ala Asn Asn Gln Tyr Ile Pro Lys Pro Lys Pro Ala Arg Ile | |
| | 305 310 315 320 | |
| 15 | Lys Lys Gly Arg Thr Arg His Ser | |
| | 325 | |
| | <210> 27 | |
| | <211> 1697 | |
| 20 | <212> DNA | |
| | <213> Homo sapiens | |
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| | aaaaggatac gggagttcct ccttgctctc gccctactc tttctggtgt tagatcgagc | 60 |
| 25 | taccctctaa aagcagttta gagtggtaaa aaaaaaaaaa aacacaccaa acgctcgagc | 120 |
| | ccacaaaagg g atg aaa ttt ctt ctg gac atc ctc ctg ctt ctc ccg tta | 170 |
| | Met Lys Phe Leu Leu Asp Ile Leu Leu Leu Leu Pro Leu | |
| | 1 5 10 | |
| | ctg atc gtc tgc tcc cta gag tcc ttc gtg aag ctt ttt att cct aag | 218 |
| 30 | Leu Ile Val Cys Ser Leu Glu Ser Phe Val Lys Leu Phe Ile Pro Lys | |
| | 15 20 25 | |
| | agg aga aaa tca gtc acc ggc gaa atc gtg ctg att aca gga gct ggg | 266 |
| | Arg Arg Lys Ser Val Thr Gly Glu Ile Val Leu Ile Thr Gly Ala Gly | |
| | 30 35 40 45 | |
| 35 | cat gga att ggg aga ctg act gcc tat gaa ttt gct aaa ctt aaa agc | 314 |

30.

| | | |
|----|---|-----|
| | His Gly Ile Gly Arg Leu Thr Ala Tyr Glu Phe Ala Lys Leu Lys Ser | |
| | 50 55 60 | |
| | aag ctg gtt ctc tgg gat ata aat aag cat gga ctg gag gaa aca gct | 362 |
| | Lys Leu Val Leu Trp Asp Ile Asn Lys His Gly Leu Glu Glu Thr Ala | |
| 5 | 65 70 75 | |
| | gcc aaa tgc aag gga ctg ggt gcc aag gtt cat acc ttt gtg gta gac | 410 |
| | Ala Lys Cys Lys Gly Leu Gly Ala Lys Val His Thr Phe Val Val Asp | |
| | 80 85 90 | |
| | tgc agc aac cga gaa gat att tac agc tct gca aag aag gtg aag gca | 458 |
| 10 | Cys Ser Asn Arg Glu Asp Ile Tyr Ser Ser Ala Lys Lys Val Lys Ala | |
| | 95 100 105 | |
| | gaa att gga gat gtt agt att tta gta aat aat gct ggt gta gtc tat | 506 |
| | Glu Ile Gly Asp Val Ser Ile Leu Val Asn Asn Ala Gly Val Val Tyr | |
| | 110 115 120 125 | |
| 15 | aca tca gat ttg ttt gct aca caa gat cct cag att gaa aag act ttt | 554 |
| | Thr Ser Asp Leu Phe Ala Thr Gln Asp Pro Gln Ile Glu Lys Thr Phe | |
| | 130 135 140 | |
| | gaa gtt aat gta ctt gca cat ttc tgg act aca aag gca ttt ctt cct | 602 |
| | Glu Val Asn Val Leu Ala His Phe Trp Thr Thr Lys Ala Phe Leu Pro | |
| 20 | 145 150 155 | |
| | gca atg acg aag aat aac cat ggc cat att gtc act gtg gct tcg gca | 650 |
| | Ala Met Thr Lys Asn Asn His Gly His Ile Val Thr Val Ala Ser Ala | |
| | 160 165 170 | |
| | gct gga cat gtc tcg gtc ccc ttc tta ctg gct tac tgt tca agc aag | 698 |
| 25 | Ala Gly His Val Ser Val Pro Phe Leu Leu Ala Tyr Cys Ser Ser Lys | |
| | 175 180 185 | |
| | ttt gct gct gtt gga ttt cat aaa act ttg aca gat gaa ctg gct gcc | 746 |
| | Phe Ala Ala Val Gly Phe His Lys Thr Leu Thr Asp Glu Leu Ala Ala | |
| | 190 195 200 205 | |
| 30 | tta caa ata act gga gtc aaa aca aca tgt ctg tgt cct aat ttc gta | 794 |
| | Leu Gln Ile Thr Gly Val Lys Thr Thr Cys Leu Cys Pro Asn Phe Val | |
| | 210 215 220 | |
| | aac act ggc ttc atc aaa aat cca agt aca agt ttg gga ccc act ctg | 842 |
| | Asn Thr Gly Phe Ile Lys Asn Pro Ser Thr Ser Leu Gly Pro Thr Leu | |
| 35 | 225 230 235 | |

| | | |
|----|---|------|
| | gaa cct gag gaa gtg gta aac agg ctg atg cat ggg att ctg act gag | 890 |
| | Glu Pro Glu Glu Val Val Asn Arg Leu Met His Gly Ile Leu Thr Glu | |
| | 240 245 250 | |
| | cag aag atg att ttt att cca tct tct ata gct ttt tta aca aca ttg | 938 |
| 5 | Gln Lys Met Ile Phe Ile Pro Ser Ser Ile Ala Phe Leu Thr Thr Leu | |
| | 255 260 265 | |
| | gaa agg atc ctt cct gag cgt ttc ctg gca gtt tta aaa cga aaa atc | 986 |
| | Glu Arg Ile Leu Pro Glu Arg Phe Leu Ala Val Leu Lys Arg Lys Ile | |
| | 270 275 280 285 | |
| 10 | agt gtt aag ttt gat gca gtt att gga tat aaa atg aaa gcg caa | 1031 |
| | Ser Val Lys Phe Asp Ala Val Ile Gly Tyr Lys Met Lys Ala Gln | |
| | 290 295 300 | |
| | taagcacct agttttctga aaactgattt accagggtta ggttgatgtc atctaatagt | 1090 |
| | gccagaattt taatgtttga acttctgttt tttctaatta tccccatttc ttcaatatca | 1150 |
| 15 | tttttgaggc ttggcagtc ttcatttact accacttggt ctttagccaa aagctgatta | 1210 |
| | catatgatat aaacagagaa atacctttag aggtgacttt aaggaaaatg aagaaaaaga | 1270 |
| | accaaaatga ctttattaaa ataatttcca agattatttg tggctcacct gaaggctttg | 1330 |
| | caaaatttgt accataaccg tttatttaac atatattttt atttttgatt gcacttaa | 1390 |
| | tttgataat ttgtgtttct ttttctgttc tacataaaat cagaaacttc aagctctcta | 1450 |
| 20 | aataaaatga aggactatat ctagtggat ttcacaatga atatcatgaa ctctcaatgg | 1510 |
| | gtaggtttca tcctacccat tgccactctg tttctgaga gatacctcac attccaatgc | 1570 |
| | caaacatttc tgcacaggga agctagaggt ggatacacgt gttgcaagta taaaagcatc | 1630 |
| | actgggattt aaggagaatt gagagaatgt accacaaaat ggcagcaata ataaatggat | 1690 |
| | cacactt | 1697 |
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| | 1 5 10 | |
| | Leu Ile Val Cys Ser Leu Glu Ser Phe Val Lys Leu Phe Ile Pro Lys | |
| 35 | 15 20 25 | |

Arg Arg Lys Ser Val Thr Gly Glu Ile Val Leu Ile Thr Gly Ala Gly
 30 35 40 45
 His Gly Ile Gly Arg Leu Thr Ala Tyr Glu Phe Ala Lys Leu Lys Ser
 50 55 60
 5 Lys Leu Val Leu Trp Asp Ile Asn Lys His Gly Leu Glu Glu Thr Ala
 65 70 75
 Ala Lys Cys Lys Gly Leu Gly Ala Lys Val His Thr Phe Val Val Asp
 80 85 90
 Cys Ser Asn Arg Glu Asp Ile Tyr Ser Ser Ala Lys Lys Val Lys Ala
 10 95 100 105
 Glu Ile Gly Asp Val Ser Ile Leu Val Asn Asn Ala Gly Val Val Tyr
 110 115 120 125
 Thr Ser Asp Leu Phe Ala Thr Gln Asp Pro Gln Ile Glu Lys Thr Phe
 130 135 140
 15 Glu Val Asn Val Leu Ala His Phe Trp Thr Thr Lys Ala Phe Leu Pro
 145 150 155
 Ala Met Thr Lys Asn Asn His Gly His Ile Val Thr Val Ala Ser Ala
 160 165 170
 Ala Gly His Val Ser Val Pro Phe Leu Leu Ala Tyr Cys Ser Ser Lys
 20 175 180 185
 Phe Ala Ala Val Gly Phe His Lys Thr Leu Thr Asp Glu Leu Ala Ala
 190 195 200 205
 Leu Gln Ile Thr Gly Val Lys Thr Thr Cys Leu Cys Pro Asn Phe Val
 210 215 220
 25 Asn Thr Gly Phe Ile Lys Asn Pro Ser Thr Ser Leu Gly Pro Thr Leu
 225 230 235
 Glu Pro Glu Glu Val Val Asn Arg Leu Met His Gly Ile Leu Thr Glu
 240 245 250
 Gln Lys Met Ile Phe Ile Pro Ser Ser Ile Ala Phe Leu Thr Thr Leu
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 Glu Arg Ile Leu Pro Glu Arg Phe Leu Ala Val Leu Lys Arg Lys Ile
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 tggagcgacc ccattacgct aaag atg aaa ggc tgg ggt tgg ctg gcc ctg 171

10

Met Lys Gly Trp Gly Trp Leu Ala Leu

1

5

ctt ctg ggg gcc ctg ctg gga acc gcc tgg gct cgg agg agc cag gat 219
 Leu Leu Gly Ala Leu Leu Gly Thr Ala Trp Ala Arg Arg Ser Gln Asp

10

15

20

25

15

ctc cac tgt gga gca tgc agg gct ctg gtg gat gaa cta gaa tgg gaa 267
 Leu His Cys Gly Ala Cys Arg Ala Leu Val Asp Glu Leu Glu Trp Glu

30

35

40

att gcc cag gtg gac ccc aag aag acc att cag atg gga tct ttc cgg 315
 Ile Ala Gln Val Asp Pro Lys Lys Thr Ile Gln Met Gly Ser Phe Arg

20

45

50

55

atc aat cca gat ggc agc cag tca gtg gtg gag gtg cct tat gcc cgc 363
 Ile Asn Pro Asp Gly Ser Gln Ser Val Val Glu Val Pro Tyr Ala Arg

60

65

70

tca gag gcc cac ctc aca gag ctg ctg gag gag ata tgt gac cgg atg 411
 Ser Glu Ala His Leu Thr Glu Leu Leu Glu Glu Ile Cys Asp Arg Met

25

75

80

85

aag gag tat ggg gaa cag att gat cct tcc acc cat cgc aag aac tac 459
 Lys Glu Tyr Gly Glu Gln Ile Asp Pro Ser Thr His Arg Lys Asn Tyr

90

95

100

105

30

gta cgt gta gtg ggc cgg aat gga gaa tcc agt gaa ctg gac cta caa 507
 Val Arg Val Val Gly Arg Asn Gly Glu Ser Ser Glu Leu Asp Leu Gln

110

115

120

ggc atc cga atc gac tca gat att agc ggc acc ctc aag ttt gcg tgt 555
 Gly Ile Arg Ile Asp Ser Asp Ile Ser Gly Thr Leu Lys Phe Ala Cys

35

125

130

135

gag agc att gtg gag gaa tac gag gat gaa ctc att gaa ttc ttt tcc 603
 Glu Ser Ile Val Glu Glu Tyr Glu Asp Glu Leu Ile Glu Phe Phe Ser
 140 145 150
 cga gag gct gac aat gtt aaa gac aaa ctt tgc agt aag cga aca gat 651
 5 Arg Glu Ala Asp Asn Val Lys Asp Lys Leu Cys Ser Lys Arg Thr Asp
 155 160 165
 ctt tgt gac cat gcc ctg cac ata tcg cat gat gag cta tgaaccactg 700
 Leu Cys Asp His Ala Leu His Ile Ser His Asp Glu Leu
 170 175 180
 10 gagcagocca cactggcttg atggatcacc ccaggaggg gaaaatggtg gcaatgcctt 760
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 10 15 20 25
 Leu His Cys Gly Ala Cys Arg Ala Leu Val Asp Glu Leu Glu Trp Glu
 30 35 40
 25 Ile Ala Gln Val Asp Pro Lys Lys Thr Ile Gln Met Gly Ser Phe Arg
 45 50 55
 Ile Asn Pro Asp Gly Ser Gln Ser Val Val Glu Val Pro Tyr Ala Arg
 60 65 70
 Ser Glu Ala His Leu Thr Glu Leu Leu Glu Glu Ile Cys Asp Arg Met
 30 75 80 85
 Lys Glu Tyr Gly Glu Gln Ile Asp Pro Ser Thr His Arg Lys Asn Tyr
 90 95 100 105
 Val Arg Val Val Gly Arg Asn Gly Glu Ser Ser Glu Leu Asp Leu Gln
 110 115 120
 35 Gly Ile Arg Ile Asp Ser Asp Ile Ser Gly Thr Leu Lys Phe Ala Cys

| | | | | | | |
|----|---|----|-----|----|-----|-----|
| | 125 | | 130 | | 135 | |
| | Glu Ser Ile Val Glu Glu Tyr Glu Asp Glu Leu Ile Glu Phe Phe Ser | | | | | |
| | 140 | | 145 | | 150 | |
| | Arg Glu Ala Asp Asn Val Lys Asp Lys Leu Cys Ser Lys Arg Thr Asp | | | | | |
| 5 | 155 | | 160 | | 165 | |
| | Leu Cys Asp His Ala Leu His Ile Ser His Asp Glu Leu | | | | | |
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| | Met Glu Val Asp Ala Pro Gly Val Asp Gly | | | | | |
| | | 1 | | 5 | | 10 |
| | CGA GAT GGT CTC CGG GAG CGG CGA GGC TTT AGC GAG GGA GGG AGG CAG | | | | | 100 |
| | Arg Asp Gly Leu Arg Glu Arg Arg Gly Phe Ser Glu Gly Gly Arg Gln | | | | | |
| 20 | | 15 | | 20 | | 25 |
| | aac ttc gat gtg agg cct cag tct ggg gca aat ggg ctt ccc aaa cac | | | | | 148 |
| | Asn Phe Asp Val Arg Pro Gln Ser Gly Ala Asn Gly Leu Pro Lys His | | | | | |
| | | 30 | | 35 | | 40 |
| | tcc tac tgg ttg gac ctc tgg ctt ttc atc ctt ttc gat gtg gtg gtg | | | | | 196 |
| 25 | Ser Tyr Trp Leu Asp Leu Trp Leu Phe Ile Leu Phe Asp Val Val Val | | | | | |
| | | 45 | | 50 | | 55 |
| | ttt ctc ttt gtg tat ttt ttg cca tgacttggtc gctgatatct aaattaagaa | | | | | 250 |
| | Phe Leu Phe Val Tyr Phe Leu Pro | | | | | |
| | | 60 | | 65 | | |
| 30 | gttggttctt gagtgaattc tgaaaatggc tacaaacttc ttgaataaag aagacaggac | | | | | 310 |
| | tctcaataga agaatttcac atctocaagg gacccttctt ttcattttac actttgttac | | | | | 370 |
| | taatttgcag aactctatta attgggtagg atttcaccca ttcctagcta agttcttaaa | | | | | 430 |
| | attaaacctt ttggttcgtg tttaaaaact ttcaaacatc tgatggcttt acaggggctg | | | | | 490 |
| | aatataaaag catttg tact t | | | | | 511 |
| 35 | | | | | | |

| | | |
|----|--|-----|
| | ctcttcacgg agocgcgcgg ctgogggggc gcaaataggg tcaactgggcc gcttggcggt | 60 |
| 25 | gtcgttgcgg taaccaggtcc gcgtgagggg ttccgggggtt ctgggcaggc aca atg | 116 |
| | Met | |
| | 1 | |
| | gcg tct cga gca ggc ccg cga gcg gcc ggc acc gac ggc agc gac ttt | 164 |
| | Ala Ser Arg Ala Gly Pro Arg Ala Ala Gly Thr Asp Gly Ser Asp Phe | |
| 30 | 5 10 15 | |
| | cag cac cgg gag cgc gtc gcc atg cac tac cag atg agt gtg acc ctc | 212 |
| | Gln His Arg Glu Arg Val Ala Met His Tyr Gln Met Ser Val Thr Leu | |
| | 20 25 30 | |
| | aag tat gaa atc aag aag ctg atc tac gta cat ctg gtc ata tgg ctg | 260 |
| 35 | Lys Tyr Glu Ile Lys Lys Leu Ile Tyr Val His Leu Val Ile Trp Leu | |

| | | | | |
|----|--|-----|-----|------|
| | 35 | 40 | 45 | |
| | ctg ctg gtt gct aag atg agc gtg gga cac ctg agg ctc ttg tca cat | | | 308 |
| | Leu Leu Val Ala Lys Met Ser Val Gly His Leu Arg Leu Leu Ser His | | | |
| | 50 | 55 | 60 | 65 |
| 5 | gat cag gtg gcc atg ccc tat cag tgg gaa tac ccg tat ttg ctg agc | | | 356 |
| | Asp Gln Val Ala Met Pro Tyr Gln Trp Glu Tyr Pro Tyr Leu Leu Ser | | | |
| | 70 | 75 | 80 | |
| | att ttg ccc tct ctc ttg ggc ctt ctc tcc ttt ccc cgc aac aac att | | | 404 |
| | Ile Leu Pro Ser Leu Leu Gly Leu Leu Ser Phe Pro Arg Asn Asn Ile | | | |
| 10 | 85 | 90 | 95 | |
| | agc tac ctg gtg ctc tcc atg atc agc atg gga ctc ttt tcc atc gct | | | 452 |
| | Ser Tyr Leu Val Leu Ser Met Ile Ser Met Gly Leu Phe Ser Ile Ala | | | |
| | 100 | 105 | 110 | |
| | cca ctc att tat ggc agc atg gag atg ttc cct gct gca cag cag ctc | | | 500 |
| 15 | Pro Leu Ile Tyr Gly Ser Met Glu Met Phe Pro Ala Ala Gln Gln Leu | | | |
| | 115 | 120 | 125 | |
| | tac cgc cat ggc aag gcc tac cgt ttc ctc ttt ggt ttt tct gcc gtt | | | 548 |
| | Tyr Arg His Gly Lys Ala Tyr Arg Phe Leu Phe Gly Phe Ser Ala Val | | | |
| | 130 | 135 | 140 | 145 |
| 20 | tcc atc atg tac ctg gtg ttg gtg ttg gca gtg caa gtg cat gcc tgg | | | 596 |
| | Ser Ile Met Tyr Leu Val Leu Val Leu Ala Val Gln Val His Ala Trp | | | |
| | 150 | 155 | 160 | |
| | cag ttg tac tac agc aag aag ctc cta gac tct tgg ttc acc agc aca | | | 644 |
| | Gln Leu Tyr Tyr Ser Lys Lys Leu Leu Asp Ser Trp Phe Thr Ser Thr | | | |
| 25 | 165 | 170 | 175 | |
| | cag gag aag aag cat aaa tgaagcctct ttggggtgaa gcctggacat cccatcga | | | 700 |
| | Gln Glu Lys Lys His Lys | | | |
| | 180 | | | |
| | atgaaaggac actagtacag cgggtccaaa atcccttctg gtgatttttag cagctgtgat | | | 760 |
| 30 | gttggtacct ggtgcagacc aggccaaagt tctggaaagc tccttttgcc atctgctgag | | | 820 |
| | gtggcaaaac tataatttat tcctggtttg ctagaactgg gtgaccgaca gctatgaac | | | 880 |
| | aaatttcagc tgtttgaagt tgaactttga gggttttctt taagaatgag ctctgtcctt | | | 940 |
| | gcctctactc ggtcattctc ccattttcca tcattaccc cttagccatt gagactaaag | | | 1000 |
| | gaaatagggg ataaatcaaa ttacttcac tctaggtcac gggtcaggaa acatttgggc | | | 1060 |
| 35 | agctgctccc ttggcagctg tggctctctc tgcaaagcat ttaattaaa aacctcaata | | | 1120 |

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aagatg

1126

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<212> PRT

<213> Homo sapiens

<400> 34

Met

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Ala Ser Arg Ala Gly Pro Arg Ala Ala Gly Thr Asp Gly Ser Asp Phe

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Gln His Arg Glu Arg Val Ala Met His Tyr Gln Met Ser Val Thr Leu

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25

30

15

Lys Tyr Glu Ile Lys Lys Leu Ile Tyr Val His Leu Val Ile Trp Leu

35

40

45

Leu Leu Val Ala Lys Met Ser Val Gly His Leu Arg Leu Leu Ser His

50

55

60

65

Asp Gln Val Ala Met Pro Tyr Gln Trp Glu Tyr Pro Tyr Leu Leu Ser

20

70

75

80

Ile Leu Pro Ser Leu Leu Gly Leu Leu Ser Phe Pro Arg Asn Asn Ile

85

90

95

Ser Tyr Leu Val Leu Ser Met Ile Ser Met Gly Leu Phe Ser Ile Ala

100

105

110

25

Pro Leu Ile Tyr Gly Ser Met Glu Met Phe Pro Ala Ala Gln Gln Leu

115

120

125

Tyr Arg His Gly Lys Ala Tyr Arg Phe Leu Phe Gly Phe Ser Ala Val

130

135

140

145

Ser Ile Met Tyr Leu Val Leu Val Leu Ala Val Gln Val His Ala Trp

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150

155

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Gln Leu Tyr Tyr Ser Lys Lys Leu Leu Asp Ser Trp Phe Thr Ser Thr

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170

175

Gln Glu Lys Lys His Lys

180

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<210> 35

<211> 2015

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<400> 35

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| | Met | |
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| 10 | ggg ccc tgg gga gag cca gag ctc ctg gtg tgg cgc ccc gag gcg gta | 104 |
| | Gly Pro Trp Gly Glu Pro Glu Leu Leu Val Trp Arg Pro Glu Ala Val | |
| | 5 10 15 | |
| | gct tca gag cct cca gtg cct gtg ggg ctg gag gtg aag ttg ggg gcc | 152 |
| | Ala Ser Glu Pro Pro Val Pro Val Gly Leu Glu Val Lys Leu Gly Ala | |
| 15 | 20 25 30 | |
| | ctg gtg ctg ctg ctg gtg ctc acc ctc ctc tgc agc ctg gtg ccc atc | 200 |
| | Leu Val Leu Leu Leu Val Leu Thr Leu Leu Cys Ser Leu Val Pro Ile | |
| | 35 40 45 | |
| | tgt gtg ctg cgc cgg cca gga gct aac cat gaa ggc tca gct tcc cgc | 248 |
| 20 | Cys Val Leu Arg Arg Pro Gly Ala Asn His Glu Gly Ser Ala Ser Arg | |
| | 50 55 60 65 | |
| | cag aaa gcc ctg agc cta gta agc tgt ttc gcg ggg ggc gtc ttt ttg | 296 |
| | Gln Lys Ala Leu Ser Leu Val Ser Cys Phe Ala Gly Gly Val Phe Leu | |
| | 70 75 80 | |
| 25 | gcc act tgt ctc ctg gac ctg ctg cct gac tac ctg gct gcc ata gat | 344 |
| | Ala Thr Cys Leu Leu Asp Leu Leu Pro Asp Tyr Leu Ala Ala Ile Asp | |
| | 85 90 95 | |
| | gag gcc ctg gca gcc ttg cac gtg acg ctc cag ttc cca ctg caa gag | 392 |
| | Glu Ala Leu Ala Ala Leu His Val Thr Leu Gln Phe Pro Leu Gln Glu | |
| 30 | 100 105 110 | |
| | ttc atc ctg gcc atg ggc ttc ttc ctg gtc ctg gtg atg gag cag atc | 440 |
| | Phe Ile Leu Ala Met Gly Phe Phe Leu Val Leu Val Met Glu Gln Ile | |
| | 115 120 125 | |
| | aca ctg gct tac aag gag cag tca ggg ccg tca cct ctg gag gaa aca | 488 |
| 35 | Thr Leu Ala Tyr Lys Glu Gln Ser Gly Pro Ser Pro Leu Glu Glu Thr | |

| | | | | | |
|----|---|------|-----|-----|--|
| | 130 | 135 | 140 | 145 | |
| | agg gct ctg ctg gga aca gtg aat ggt ggg ccg cag cat tgg cat gat | 536 | | | |
| | Arg Ala Leu Leu Gly Thr Val Asn Gly Gly Pro Gln His Trp His Asp | | | | |
| | 150 | 155 | 160 | | |
| 5 | ggg cca ggg gtc cca cag gcg agt gga gcc cca gca acc ccc tca gcc | 584 | | | |
| | Gly Pro Gly Val Pro Gln Ala Ser Gly Ala Pro Ala Thr Pro Ser Ala | | | | |
| | 165 | 170 | 175 | | |
| | ttg cgt gcc tgt gta ctg gtg ttc tcc ctg gcc ctc cac tcc gtg ttc | 632 | | | |
| | Leu Arg Ala Cys Val Leu Val Phe Ser Leu Ala Leu His Ser Val Phe | | | | |
| 10 | 180 | 185 | 190 | | |
| | gag ggg ctg gcg gta ggg ctg cag cga gac cgg gct cgg gcc atg gag | 680 | | | |
| | Glu Gly Leu Ala Val Gly Leu Gln Arg Asp Arg Ala Arg Ala Met Glu | | | | |
| | 195 | 200 | 205 | | |
| | ctg tgc ctg gct ttg ctg ctc cac aag ggc atc ctg gct gtc agc ctg | 728 | | | |
| 15 | Leu Cys Leu Ala Leu Leu Leu His Lys Gly Ile Leu Ala Val Ser Leu | | | | |
| | 210 | 215 | 220 | 225 | |
| | tcc ctg cgg ctg ttg cag agc cac ctt agg gca cag gtg gtg gct ggc | 776 | | | |
| | Ser Leu Arg Leu Leu Gln Ser His Leu Arg Ala Gln Val Val Ala Gly | | | | |
| | 230 | 235 | 240 | | |
| 20 | tgt ggg atc ctc ttc tca tgc atg aca cct cta ggc atc ggg ctg ggt | 824 | | | |
| | Cys Gly Ile Leu Phe Ser Cys Met Thr Pro Leu Gly Ile Gly Leu Gly | | | | |
| | 245 | 250 | 255 | | |
| | gca gct ctg gca gag tcg gca gga cct ctg cac cag ctg gcc cag tct | 872 | | | |
| | Ala Ala Leu Ala Glu Ser Ala Gly Pro Leu His Gln Leu Ala Gln Ser | | | | |
| 25 | 260 | 265 | 270 | | |
| | gtg cta gag ggc atg gca gct ggc acc ttt ctc tat atc acc ttt ctg | 920 | | | |
| | Val Leu Glu Gly Met Ala Ala Gly Thr Phe Leu Tyr Ile Thr Phe Leu | | | | |
| | 275 | 280 | 285 | | |
| | gaa atc ctg ccc cag gag ctg gcc agt tct gag caa agg atc ctc aag | 968 | | | |
| 30 | Glu Ile Leu Pro Gln Glu Leu Ala Ser Ser Glu Gln Arg Ile Leu Lys | | | | |
| | 290 | 295 | 300 | 305 | |
| | gtc att ctg ctc cta gca ggc ttt gcc ctg ctc act ggc ctg ctc ttc | 1016 | | | |
| | Val Ile Leu Leu Leu Ala Gly Phe Ala Leu Leu Thr Gly Leu Leu Phe | | | | |
| | 310 | 315 | 320 | | |
| 35 | atc caa atc tagggggctt caagagaggg gcaggggaga ttgatgatca ggtgc | 1070 | | | |

Ile Gln Ile

cccgtgttctc ccttcctcc cccagttgtg gggaatagga aggaaagggg aagggaata 1130
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 15 gaatatgggg acatggacat ggtgtcccat gccagatga taaacactga gctgccaaaa 1850
 ctttttttta aatacacccg aggagcccaa gggggaaggg caatgcctac cccagcgtt 1910
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25 <400> 36

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 35 40 45
 Cys Val Leu Arg Arg Pro Gly Ala Asn His Glu Gly Ser Ala Ser Arg
 35 50 55 60 65

Gln Lys Ala Leu Ser Leu Val Ser Cys Phe Ala Gly Gly Val Phe Leu
 70 75 80
 Ala Thr Cys Leu Leu Asp Leu Leu Pro Asp Tyr Leu Ala Ala Ile Asp
 85 90 95
 5 Glu Ala Leu Ala Ala Leu His Val Thr Leu Gln Phe Pro Leu Gln Glu
 100 105 110
 Phe Ile Leu Ala Met Gly Phe Phe Leu Val Leu Val Met Glu Gln Ile
 115 120 125
 Thr Leu Ala Tyr Lys Glu Gln Ser Gly Pro Ser Pro Leu Glu Glu Thr
 10 130 135 140 145
 Arg Ala Leu Leu Gly Thr Val Asn Gly Gly Pro Gln His Trp His Asp
 150 155 160
 Gly Pro Gly Val Pro Gln Ala Ser Gly Ala Pro Ala Thr Pro Ser Ala
 165 170 175
 15 Leu Arg Ala Cys Val Leu Val Phe Ser Leu Ala Leu His Ser Val Phe
 180 185 190
 Glu Gly Leu Ala Val Gly Leu Gln Arg Asp Arg Ala Arg Ala Met Glu
 195 200 205
 Leu Cys Leu Ala Leu Leu Leu His Lys Gly Ile Leu Ala Val Ser Leu
 20 210 215 220 225
 Ser Leu Arg Leu Leu Gln Ser His Leu Arg Ala Gln Val Val Ala Gly
 230 235 240
 Cys Gly Ile Leu Phe Ser Cys Met Thr Pro Leu Gly Ile Gly Leu Gly
 245 250 255
 25 Ala Ala Leu Ala Glu Ser Ala Gly Pro Leu His Gln Leu Ala Gln Ser
 260 265 270
 Val Leu Glu Gly Met Ala Ala Gly Thr Phe Leu Tyr Ile Thr Phe Leu
 275 280 285
 Glu Ile Leu Pro Gln Glu Leu Ala Ser Ser Glu Gln Arg Ile Leu Lys
 30 290 295 300 305
 Val Ile Leu Leu Leu Ala Gly Phe Ala Leu Leu Thr Gly Leu Leu Phe
 310 315 320
 Ile Gln Ile